Timeliness and Equity as Overlooked Quality Domains:

Racial/Ethnic Disparities in Timeliness of Adjuvant Chemotherapy Receipt for Stage III Colon Cancer

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Dedication

To my parents, for the sacrifice it took to get us here.

ABSTRACT

Consensus and evidence-based guidelines or quality measures provide treatment recommendations to promote standardized, high-quality health care. This research focused on a specific guideline which recommends stage III colon cancer patients to receive adjuvant chemotherapy within 4 months of diagnosis. It was endorsed by the National Quality Forum (NQF) in 2007 and has yet to be investigated for two important yet understudied health care quality domains: timeliness and racial/ethnic equity of care. Data from the linked Surveillance and Epidemiology and End Results (SEER) cancer registry and Medicare claims were used to investigate the following topics: 1. disparities in guideline-concordant adjuvant chemotherapy receipt, distinguishing between omitted and delayed chemotherapy as forms of guideline discordance; 2. racial/ethnic disparities in timeliness of adjuvant chemotherapy receipt, while assessing wait time disparities before and after tumor resection; 3. the impact of the guideline in changing rates of timely adjuvant chemotherapy receipt and racial differences in trends over time. This research provides important new insights into racial/ethnic equity of cancer care for White, Black, Hispanic, and Asian/Pacific Islander patients, with a nuanced focus on timeliness and delay that is overlooked in the quality of care literature.

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CHAPTER 1: INTRODUCTION

SPECIFIC AIMS

Timeliness and equity are two important health care quality domains that are not often considered together in research. To add to this literature, this dissertation focused on racial/ethnic disparities in timeliness of adjuvant chemotherapy receipt for colon cancer, where delaying chemotherapy by a matter of weeks significantly reduces patient survival [1]. Disparities in timeliness of care have yet to be investigated in the context of a guideline endorsed by the National Quality Forum (NQF) in 2007. This guideline recommends initiating adjuvant chemotherapy within 4 months of diagnosis for stage III colon cancer patients. Using this guideline, the following were the 3 aims of this research:

Aim 1. To investigate racial/ethnic disparities in guideline-concordant adjuvant chemotherapy receipt, while distinguishing the guideline-discordant groups of omitted and delayed chemotherapy.

Aim 2. To investigate racial/ethnic disparities in wait times to initiate adjuvant chemotherapy after diagnosis, while breaking down this interval to assess wait time disparities within treatment sub-intervals (before and after tumor resection).

Aim 3. To investigate the impact of the NQF-endorsed guideline on timely adjuvant chemotherapy receipt, and racial differences in these trends over a 10-year time period.

To investigate these aims, we used the linked Surveillance and Epidemiology and End Results (SEER) cancer registry and Medicare dataset (2003-2014). We used three of six health care quality domains described in *Crossing the Quality Chasm* to inform examination of quality of care: effective, timely, and equitable care [2]. Collectively, the

products of this research advance our understanding of racial/ethnic disparities in colon cancer quality of care, specifically in timeliness of adjuvant chemotherapy receipt for White, Black, Hispanic, and Asian/Pacific Islander patients.

BACKGROUND

Colorectal cancer is one of the most commonly diagnosed cancers and the second leading cause of cancer death in the U.S. [3]. It is most frequently diagnosed among those aged 65-74, with higher incidence rates and death rates among men and Black men and women [3]. Over time, the number of new cases and death rates have been decreasing [3].

Colon cancer is cancer that has originated in the colon/large bowel, which is the first 6 feet of the large intestine, and is staged from 0 to IV [3, 4]. The focus of this dissertation is on patients diagnosed with stage III colon cancer (IIIA, IIIB, IIIC), where the cancer has spread from the origin to nearby lymph nodes (regional stage). Thirty-five percent of colorectal cancer cases are regional and 5-year relative survival is 71.1% [3].

Established treatment for stage III colon cancer includes surgical resection of the tumor followed by adjuvant chemotherapy, which significantly improves patient survival [5]. The vast majority of patients diagnosed with stage III colon cancer undergo surgery to remove the tumor [6], while rates of treatment with adjuvant chemotherapy have been varied and have increased over time [7-10].

One of the first studies on patterns of adjuvant chemotherapy receipt used SEER-Medicare data from 1991-1996, and found 55% of patients ages 65+ received adjuvant chemotherapy within 3 months of surgery [7]. This rate increased to 64% in a study using 1991-2005 data [11]. In these studies, the rate is higher for the younger age groups, and is confirmed by a systematic review that suggested 70-76% of patients between ages 65 and 75 received adjuvant chemotherapy [12]. Studies have found that median time to initiate chemotherapy is 5-6 weeks after surgery [7, 11].

Although delays to surgical resection have not shown to negatively impact patient survival [13], timely initiation of adjuvant chemotherapy is shown to be critical for

patient outcomes [1]. A 2011 systematic review and meta-analysis found that prolonged time to initiate chemotherapy is associated with significantly reduced overall and disease-free survival among patients with resected colorectal cancer [1]. It found that relative overall survival decreased by 14% for every 4-week delay after surgery. Beyond survival, qualitative studies have found that prolonged wait times to start chemotherapy can increase uncertainty and anxiety for patients and caregivers [14, 15].

ADJUVANT CHEMOTHERAPY GUIDELINE

Clinical trials from the 1980's provided strong evidence of survival benefit for stage III colon cancer patients who were treated with adjuvant chemotherapy compared to those who did not receive it [5]. Based on these studies, the National Institutes of Health Consensus Development Conference released a statement in 1990 recommending adjuvant chemotherapy for stage III colon cancer patients, who have high risk of cancer recurrence after tumor resection [5].

Since then, observational studies have confirmed clinical trial findings [8, 16-18], and guidelines recommending adjuvant chemotherapy have been created by organizations such as National Comprehensive Cancer Network (NCCN), American Society of Clinical Oncology (ASCO), and American College of Surgeons Commission on Cancer (CoC). The latest guideline put together by these organizations was endorsed by the National Quality Forum (NQF) in 2007 (NQF #0223). Compared to prior guidelines, it includes a recommended timeframe for initiating chemotherapy. The guideline states: Adjuvant chemotherapy is recommended or administered within 4 months (120 days) of diagnosis for patients under the age of 80 with AJCC [American Joint Committee on Cancer] Stage III (lymph node positive) colon cancer [19]. The timeframe takes into account the time needed for surgery and recovery from complications [20].

The guideline is a hospital or systems-level performance measure, and it was validated using National Cancer Data Base (NCDB) data. NQF lists CoC as the steward of this measure, which was submitted to NQF in early 2005 for consideration and endorsed on February 28, 2007 as an accountability measure. CoC creates three main types of measures: 1. accountability (strong evidence from multiple randomized control trials (RCTs), used for public reporting, payment incentive programs), 2. quality improvement (evidence from non-RCT experimental studies, used for internal performance monitoring), and 3. surveillance (limited evidence, used to identify status quo, monitor patterns) [21]. While some CoC measures have an expected performance rate, the specific guideline used in this dissertation does not list an expected performance rate; however, measures are not meant to require a 100% performance rate [22].

RACIAL/ETHNIC DISPARITIES IN HEALTH CARE & OUTCOMES

Colorectal Cancer Screening Disparities

Racial/ethnic disparities along the cancer care continuum are well known, from cancer screening rates to survival rates. Screening for colorectal cancer is recommended to begin at age 50, with some organizations recommending that screening begin at earlier ages such as 40 or 45 for the African American population [23]. Black patients have lower colon cancer screening rates and consequently are diagnosed with more advanced stages of cancer [23-25]. Multiple physician and patient factors play a role in these disparities, with health systems having the ability to ameliorate gaps in access by incorporating use of tailored education and patient navigator systems [23]. Colorectal cancer screening programs implemented in New York City and in Delaware that also specifically addressed disparities were able to eliminate screening disparities between Black and White populations [26, 27]. In addition, one of the programs eliminated

disparities in cancer incidence and advanced cancer stage, and almost equalized mortality differences (but not survival differences) [26].

Survival Disparities

Colon cancer survival disparities are well known. Black patients have worse overall and colon cancer-specific survival compared to White patients [28-34]. The absolute difference in demographics-adjusted 5-year survival rates was close to 10% from 1991 to 2005 [29, 30], and was 4.3% after matching on clinical and treatment factors [30]. Various factors are associated with these survival disparities, including socioeconomic status differences [28, 35], comorbidity and advanced cancer stage [30], treatment differences [30], and hospital factors [34].

Treatment Disparities

Survival disparities among stage III colon cancer patients have shown to be largely attributable to socioeconomic differences [28], while some studies indicate that treatment differences may also explain some of the Black-White survival differences [29, 30]. Known racial disparities in treatment include delays to surgical resection of the tumor and not receiving adjuvant chemotherapy as part of the treatment [13, 36].

Surgical Resection of Tumor

Disparities in getting surgery for stage III colon cancer have not been found [6]. However, Black patients have been shown to have a higher rate of unplanned (emergency or urgent) colon cancer resections [37-39], which is associated with worse disease-free survival [38]. A few studies have also found racial disparities in delays from diagnosis to surgical resection, where Black and Hispanic patients had longer wait times to surgery [13, 40, 41].

Adjuvant Chemotherapy Receipt

In a systematic review, 7 of 9 studies that assessed disparities found a disparity in chemotherapy receipt between White and Black patients, but not for other minority groups such as Hispanic and Asian patients [12]. While some studies have shown that this disparity has reduced over time [8, 10], one study found a more recent widening of the disparity in 2010 [42]. Some studies where all patients received adjuvant chemotherapy do not show racial survival disparities [36, 43, 44], with one study showing that survival differences persisted even after receiving the same treatment (however, this study could not control for comorbidity) [45].

GAPS IN THE LITERATURE

Racial/ethnic disparities in timeliness of care remains an understudied area of research, particularly for colon cancer quality of care. Not only is receiving chemotherapy important to improve patient survival, but the timing when chemotherapy is started is also important for patient survival. This makes disparities in chemotherapy receipt and timeliness particularly important to address. Early studies have consistently shown that Black patients were less likely than White patients to receive chemotherapy for colon cancer [7, 9, 11, 12, 46]; however, very little is known about disparities in chemotherapy delays, despite other well-known disparities such as delays to surgical resection [13, 40, 41].

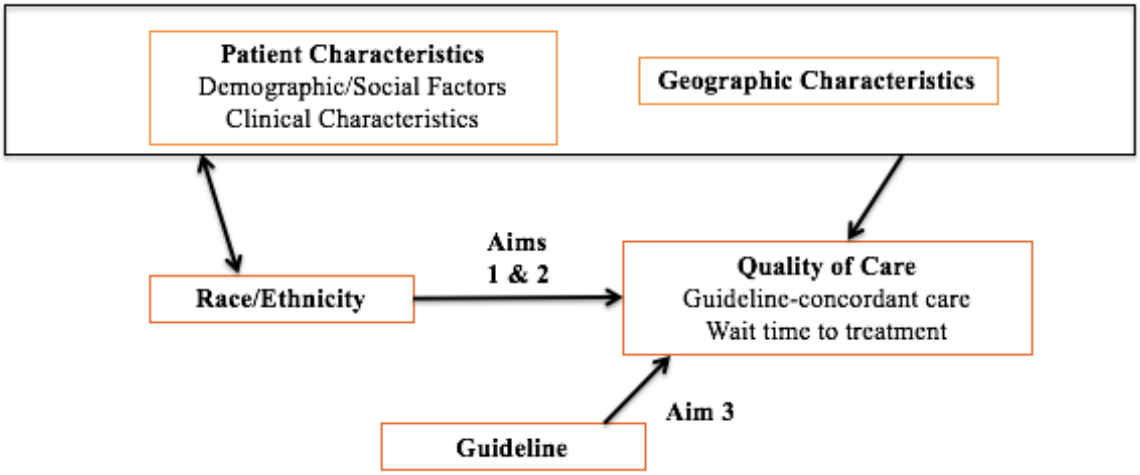
Studies have indicated that Black patients were more likely to receive delayed adjuvant chemotherapy for breast cancer [47, 48], but only two studies have currently assessed disparities in delays for colon cancer, and did not find disparities in timeliness of chemotherapy receipt [36, 44]. These studies were conducted with cohorts diagnosed

prior to the most updated guideline and do not assess disparities in timeliness of care for Hispanic or Asian minority populations.

Studies have yet to assess disparities in timeliness of chemotherapy receipt using the current guideline or with a contemporary study cohort. Additionally, the current guideline is reported by health systems with a binary approach, so that delays are not specifically assessed. Given the importance of timeliness of chemotherapy receipt for patient survival, this research aimed to add to the scarce literature on timeliness and equity by assessing racial/ethnic disparities in timeliness of adjuvant chemotherapy receipt for stage III colon cancer.

CONCEPTUAL FRAMEWORK

Figure 1. Conceptual Model of Factors Associated with Timeliness of Care



The Behavioral Model of Health Services Use was used to inform the conceptual framework of this dissertation (Figure 1) [49, 50]. Our model attempts to account for potential confounders to the relationship between race/ethnicity and timely adjuvant chemotherapy receipt. The conceptual model includes sociodemographic factors such as age, marital status, and socioeconomic status; clinical characteristics such as comorbidity; and geographic factors such as rural/urban residence.

Sociodemographic factors, including age, socioeconomic status, and marital status, are associated with race/ethnicity and with adjuvant chemotherapy receipt. Increased age is strongly associated with decreased adjuvant chemotherapy receipt [7, 9, 11], yet the youngest group of Medicare Black patients (66-70 years) are less likely to receive adjuvant chemotherapy compared to White patients [46]. Studies have found that socioeconomic status (e.g. median income in Census tract of residence) affects chemotherapy receipt [7, 12, 46], and those who are married (a proxy for social support) are more likely to receive chemotherapy [9, 11, 12].

Clinical factors including comorbidity and hospital length of stay after surgery (LOS) are associated with race/ethnicity and adjuvant chemotherapy receipt. Comorbidity is strongly associated with chemotherapy; use diminishes with higher levels of comorbidity [7, 9, 11, 12]. LOS after surgical resection could be indication of a couple issues affecting chemotherapy receipt such as underlying poor health status, occurrence of surgical or postsurgical complications, or lack of a caregiver at home [46, 51]. LOS after surgery has previously shown to greatly contribute to disparity in chemotherapy receipt between Black and White patients [46]. Some studies have shown that a few hospital and provider factors are associated with chemotherapy use [12, 46, 47, 52]; however only contribute to a small portion of the racial disparity in adjuvant chemotherapy receipt [46].

SUMMARY OF RESEARCH

Equity in timeliness of health care is understudied, particularly in colon cancer research. Disparities have yet to be investigated in the context of a current guideline that recommends adjuvant chemotherapy within 4 months of stage III colon cancer diagnosis [19]. We first investigated racial/ethnic variation in guideline concordance and distinguished between the guideline-discordant categories of omitted chemotherapy and delayed chemotherapy receipt, which is not typically done in the research literature or in quality measure reporting.

Next, we investigated disparities in specific treatment time intervals to further elucidate where delays could be occurring. Within the timeline between diagnosis and chemotherapy initiation, there are two main sub-intervals where delay could have occurred, before or after surgery to remove the tumor. Whether treatment wait time disparities occurred in either or both of these sub-intervals was investigated. We aimed to

better understand racial/ethnic disparities in timely chemotherapy receipt in the context of these multiple treatment time intervals.

Our last study investigated the impact of the current guideline of timely adjuvant chemotherapy initiation. There is little evidence on practice variations over time or across racial groups in response to the addition of the timeframe for the chemotherapy recommendation. We aimed to demonstrate patterns of timely chemotherapy receipt over a 10-year period, and whether rates improved after the current guideline was endorsed by the NQF in 2007.

CHAPTER 2: (Paper 1) Racial/Ethnic Disparities in Timeliness of Adjuvant Chemotherapy for Stage III Colon Cancer: Distinguishing Delay from Omission using a Quality Measure

OVERVIEW

Background

Timeliness and equity are two important health care quality domains that are not often considered together in research. To examine these domains, this research focused on a guideline which recommends initiating adjuvant chemotherapy within 4 months of diagnosis for stage III colon cancer. Racial/ethnic disparities in guideline concordance were investigated, while distinguishing two forms of guideline discordance, omitted and delayed chemotherapy.

Methods

Linked Surveillance and Epidemiology and End Results (SEER) registry and Medicare claims data were used. Patients diagnosed with stage III colon cancer during 2007-2013 were included. The categorical outcome was defined as three levels of chemotherapy receipt: within 4 months of diagnosis; after 4 months of diagnosis; never received. The key independent variable was race/ethnicity. Multinomial logistic regression models adjusted for covariates. All significance tests were two-sided.

Results

Overall, 71% received chemotherapy within guideline parameters, 7% received it late, and 21% not at all, with variation by race/ethnicity. Compared to White patients, Black patients were less likely to receive chemotherapy within four months of diagnosis. They were more likely to have chemotherapy delayed (RRR=1.69; 95% CI=1.21-2.36), or to never receive it (RRR=1.42; 95% CI=1.12-1.80). Following adjustment, no significant disparities were observed for Hispanic or Asian populations.

Conclusions

This population-based study found opportunity to increase guideline-concordant delivery of chemotherapy for stage III colon cancer. Black patients were more likely than White patients to receive guideline-discordant care, both in delayed chemotherapy and in never receiving it. Efforts to address disparities need to focus on both forms of guideline discordance.

INTRODUCTION

Colorectal cancer is one of the most commonly diagnosed cancers and is the second leading cause of cancer death in the U.S. [37]. This research focused on stage III colon cancer, where the cancer has spread from the origin to nearby lymph nodes (regional stage). Thirty-five percent of colorectal cancer cases are regional and 5-year relative survival is 71.1% [3]. Established treatment for stage III colon cancer includes surgical resection of the tumor and associated lymph nodes followed by adjuvant chemotherapy. Since there is a high risk of cancer recurrence after tumor removal, World Health Organization (WHO) guidelines recommend chemotherapy, shown to decrease risk of recurrence and improve patient survival rates [5, 8, 16-18, 53].The vast majority of patients diagnosed with stage III colon cancer undergo surgery to remove the tumor because surgery is usually necessary to identify lymph node metastases and correctly stage the patient [6]; on the other hand, rates of treatment with adjuvant chemotherapy have been varied and have increased over time [7-10].

The timing of adjuvant chemotherapy initiation is also critical for patient health outcomes. A systematic review and meta-analysis found that relative overall survival decreased by 14% for every 4-week delay after surgery among patients with resected colorectal cancer [1]. Delays to initiate chemotherapy can also increase uncertainty and anxiety for patients and caregivers [14, 15]. For this study, we focused on a guideline which recommends a timeframe within which stage III colon cancer patients should receive adjuvant chemotherapy (within 4 months of diagnosis). However, the guideline is a performance measure reported by health systems as a binary measure. With this approach, the extent of guideline discordance stemming from delay versus omitted chemotherapy is not assessed. The guideline was endorsed by the National Quality

Forum (NQF) in 2007 and has yet to be investigated in the context of two important health care quality domains not often examined together: racial/ethnic equity in timeliness of recommended care.

Racial/ethnic disparities along the colon cancer care continuum have been reported, particularly for Black patients [13, 25, 28, 30, 33, 35, 40, 41, 46, 54]. Early studies consistently showed that Black patients with stage III colon cancer were less likely than White patients to receive adjuvant chemotherapy [11, 12]. However, very little is known about racial disparities in the timeliness of chemotherapy initiation. Only two studies that we know of have currently assessed disparities in chemotherapy delays for colon cancer, and did not find disparities in timeliness of chemotherapy receipt [36, 44]. These studies did not assess disparities in the NQF-endorsed guideline, as they were conducted with cohorts diagnosed prior to the guideline, and also did not assess disparities in timeliness of care for Hispanic or Asian minority populations.

Given the importance of timeliness of chemotherapy receipt for patient survival, this research aimed to add to the scarce literature on timeliness and equity. We investigated racial/ethnic variation in guideline concordance and distinguished between guideline discordance stemming from omitted chemotherapy and delayed chemotherapy, which is not typically done in the research literature or in quality measure reporting.

METHODS

Data Source

We used data sponsored by the National Cancer Institute (NCI) – the linked Surveillance and Epidemiology and End Results (SEER) cancer registry and Medicare claims dataset (2006-2014).

Study Population

The NQF-endorsed guideline (2007-present) eligibility criteria were used to inform eligibility for this study population [19]. The cohort included persons aged 66-79 with a stage III colon cancer diagnosis between January 1, 2007 and December 31, 2013. Colon cancer diagnoses were identified with ICD-O-3 site codes: C18.0, C18.2-C18.9. Stage IIIs were identified with American Joint Committee on Cancer (AJCC) Stage Group variables from SEER, 6th edition (codes 50-54) and 7th edition (codes 500-542). We further restricted the cohort to those that had a colon resection, identified by ICD-9-CM procedure codes beginning with 45.7, 45.8, and 17.3. Those likely to have complete Medicare fee-for-service (FFS) claims, with both Parts A and B coverage for at least one year after diagnosis or until death were included. FFS A+B claims one year prior to diagnosis were also required to obtain a complete comorbidity profile [55, 56]. Additional standard exclusions consisted of: health maintenance organization (HMO) enrollment, diagnosis after autopsy/death certificate, death within 4 months of diagnosis, any prior cancer diagnoses, any colorectal resection prior to diagnosis or more than 12 months after diagnosis, chemotherapy claims before diagnosis or surgery. After applying the eligibility criteria, the final study population number was 5,166. See Appendix for selection details.

Dependent Variables

The main dependent variable was a categorical measure with 3 levels of chemotherapy receipt: (1) receipt within 4 months of diagnosis (guideline-concordant), (2) receipt after 4 months of diagnosis (guideline-discordant, delayed receipt), and (3) no chemotherapy receipt (guideline-discordant, omitted). To allow for comparison with published studies, we also created two binary variables: (1) guideline-concordant receipt

versus discordant receipt and (2) adjuvant chemotherapy receipt regardless of timing versus not received.

Diagnosis and chemotherapy dates were identified using Medicare sources. The diagnosis date is defined as the earliest claim date containing a colon cancer ICD-9-CM diagnosis code (153.0-153.4, 153.6-153.9). The chemotherapy date is defined as the earliest claim date containing a colon cancer diagnosis code and a chemotherapy code. We used chemotherapy codes similar to other published studies during this time period [57] (see Appendix for list of codes). Persons first receiving chemotherapy more than 12 months after diagnosis were classified as not receiving chemotherapy.

Key Independent Variable

The key independent variable, race/ethnicity, was obtained from SEER sources with the following categories: Non-Hispanic White, Black, Hispanic, and Asian/Pacific Islander. Very small numbers (<11) Hispanic Black and Hispanic Asian/Pacific Islanders were grouped with their respective race categories.

Covariates

Sociodemographic variables obtained from SEER sources included gender (male, female), age (66-69, 70-74, 75-79), marital status (married/domestic partner or unmarried), census tract poverty (0% to <10% poverty, 10% to <20%, ≥20%), and residence (metropolitan or non-metropolitan) [58]. Clinical variables obtained from SEER sources included year of colon cancer diagnosis (2007-2013), tumor grade (well/moderately differentiated or poorly/undifferentiated/unknown), tumor location (left or right side of colon). Medicare data were used to obtain length of stay (LOS) after surgery (continuous), and to create the Charlson comorbidity index (CCI; 0, 1, 2, or 3+) [55, 56].

Statistical Methods

We first conducted chi-square tests to assess racial/ethnic variations in the binary and categorical dependent variables. For full adjustment, we used a multinomial logistic regression model of the categorical dependent variable on race/ethnicity and all covariates. This model estimated adjusted racial/ethnic differences in likelihood of delayed or no chemotherapy, with guideline-concordant chemotherapy as the reference outcome. We reported results as relative risk ratios (RRRs). All significance tests were two-sided. All data management and analyses were conducted using SAS 9.4 (SAS Institute, Cary NC).

RESULTS

Study characteristics are presented in Table 1. The majority of the study population was White and aged 70 or older. Important differences in population characteristics across racial/ethnic groups were observed, where a higher percentage of Black patients were living in high poverty census tracts, unmarried, exhibited severe comorbidity, and had hospital stays greater than 14 days. Higher percentages of Asian and Hispanic patients lived in metropolitan areas.

The descriptive results of the two binary dependent variables are presented in Table 1. Overall, 79% of the surgically-resected stage III colon cancer patients in this study received adjuvant chemotherapy, regardless of timing. The remaining 21% did not receive chemotherapy. Overall, 71% of the patient population were compliant with guideline recommendations to initiate chemotherapy within 4 months of diagnosis. The remaining 29% either had delayed chemotherapy or did not receive chemotherapy. However, the majority of guideline discordance stemmed from omitted chemotherapy, since 91% of those that received chemotherapy initiated it within 4 months of diagnosis.

Patterns of chemotherapy delay and omission differed importantly across racial/ethnic groups, as indicated by the categorical measure for guideline concordance (Figure 2). Forty-three percent of Black patients did not receive adjuvant chemotherapy within 4 months of diagnosis, compared to the other racial/ethnic groups (27-30% guideline discordance). A majority of the guideline discordance stemmed from not receiving any chemotherapy, where 31% of Black patients were not treated with adjuvant chemotherapy compared to 19-21% of the other racial/ethnic groups. There were also important racial/ethnic differences in guideline discordance stemming from delay, where 12% of Black patients received adjuvant chemotherapy after 4 months of diagnosis, compared to 7% of White patients, 10% of Hispanic patients, and 9% of Asian patients that received delayed chemotherapy. Black patients were therefore less likely to be treated with adjuvant chemotherapy and when they did receive it, were more likely to be delayed.

Table 2 presents multinomial logistic regression estimates that are unadjusted, adjusted for sociodemographic factors only, and then fully adjusted (all covariates). The estimates reflect the likelihood of delayed chemotherapy and likelihood of omitted chemotherapy, versus the reference outcome of guideline-concordant chemotherapy. The fully adjusted results indicated that compared to White patients, Black patients were more likely to have delayed chemotherapy (RRR=1.69; 95% CI=1.21-2.36), and more likely to never receive chemotherapy (RRR=1.42; 95% CI=1.12-1.80) rather than receive treatment as recommended by the guideline. Hispanic and Asian differences were not statistically significant.

DISCUSSION

A guideline based on clinical consensus and the published literature promotes offering adjuvant chemotherapy to patients within 4 months of stage III colon cancer diagnosis [19]. This population-based study was the first to assess racial/ethnic disparities in this guideline, while breaking down guideline discordance into omitted and delayed chemotherapy. There was evidence of disparities in both forms of guideline discordance, indicating an opportunity to increase guideline-concordant delivery of chemotherapy. Specifically, we found that Black patients were more likely than White patients to receive guideline-discordant care, both in delayed chemotherapy and in never receiving it.

Our finding that Black patients were less likely to receive adjuvant chemotherapy is consistent with several other SEER-based studies [11, 12, 42]. However, our finding that Black patients were more likely to receive delayed chemotherapy is different from results of the two previous studies on delay [36, 44]. It is possible this is due to differences in the study populations and methods used. Studies of chemotherapy delays in other patient populations (e.g. breast cancer patients) indicate that Black patients are more likely to receive delayed adjuvant chemotherapy [47, 48].

There are limited research studies on timeliness of care, where methodologies and definitions of delay are varied since dates of events are challenging to obtain. Also, there is a general lack of quality measures that specifically define delayed care, even though timeliness is a quality domain [2, 59]. Quality measures with recommended timeframes of care such as the one assessed in this study can guide a more standardized definition and reporting of timeliness and delay. However, the guideline in this study is reported by health systems with a binary approach, as the percentage of patients that received chemotherapy within 4 months of diagnosis. Given that delaying chemotherapy by a

matter of weeks significantly reduces survival, our findings underscore the importance of separately quantifying delayed and omitted chemotherapy. Health systems may want to understand the extent of each within the organization to better understand strategies to improve timely chemotherapy receipt.

There are also limited research studies on racial/ethnic equity in timeliness of care. Our findings indicate that equity in timeliness should be assessed, particularly for treatments where timeliness is associated with better patient survival rates. Our findings also emphasize that racial disparities in omitted chemotherapy continue to persist in a contemporary study cohort. Given that Black-White disparities in colon cancer survival rates are partly explained by differences in receiving adjuvant chemotherapy [30], disparities in this form of guideline discordance continues to need attention.

Discordance that is due to logistics and other non-clinical barriers should be better understood, particularly mutable access barriers such as structural, financial, and cognitive/communication barriers that are associated with health care disparities [60, 61]. Racial disparities in this quality measure should also be considered in quality improvement efforts and interventions. While some interventions have been conducted to address specific barriers to timely care [62, 63], more studies are needed to understand ways to reduce these disparities in cancer quality of care [64-66].

This study has limitations that must be acknowledged. We cannot determine that a patient's race is the cause of differences in guideline concordance, but we can determine that race is associated with delayed care and omitted chemotherapy even after controlling for confounders. As with most observational studies, we could not control for all possible patient, provider, and structural confounders. Additionally, the guideline considers those who had chemotherapy recommended but did not receive it as guideline-concordant.

Since we were unable to identify these cases, there is a possibility of misclassification. If a patient is recommended for chemotherapy and did not receive it, understanding underlying causes and reducing disparities here is still important. Data were also not available to determine which patients did not receive chemotherapy due to not being good candidates for it. We attempted to account for this by excluding those that died within 4 months of diagnosis (a guideline exclusion criterion), and controlled for pre-diagnosis comorbidity and hospital LOS. We did not find that these factors changed the results. Also, findings may not be generalizable to younger populations. However, the target population for this quality measure is the elderly below age 80.

Despite limitations, this study has considerable strengths. We used NCI-sponsored linked SEER-Medicare data, which are population-based data sources covering approximately 28% of the U.S. population (SEER) and the majority of elderly Americans (Medicare). We used a guideline that is still current and has not been previously investigated for racial/ethnic disparities. Contemporary patterns of chemotherapy omission are limited in existing literature, and most studies have not assessed for disparities in delayed chemotherapy receipt among colon cancer patients. To provide insight into guideline discordance, we used a categorical outcome to distinguish between those that received delayed chemotherapy and those that were not treated with chemotherapy. This study also included Hispanic and Asian/Pacific Islander patients, which are traditionally understudied populations in health services research.

This population-based study found evidence of racial disparities in guideline-concordant care for stage III colon cancer. Black-White disparities in both delayed and omitted chemotherapy were contributing to guideline discordance, with most of the discordance stemming from omission. We found that chemotherapy was more likely to

be omitted or delayed rather than timely for Black patients compared to White patients. To address disparities, efforts focusing on both forms of guideline discordance are important, particularly since timely chemotherapy receipt reduces cancer recurrence and improves survival for patients with stage III colon cancer.

Table 1. Sociodemographic and Clinical Characteristics of Patients with Stage III Colon Cancer by Race/Ethnicity, Ages 66-79, SEER-Medicare 2007-2013 Diagnoses

	White N=4018 78%	**Black** N=512 10%	**Hispanic** N=304 6%	**Asian/PI** N=332 6%	**Total** N=5166 100%	
	N (%)	N (%)	N (%)	N (%)	N (%)	P-value
Adjuvant Chemotherapy Receipt	3208 (80)	352 (69)	246 (81)	262 (79)	4,068 (79)	<.0001
Guideline-Concordant Adjuvant Chemotherapy Receipt	2,942 (73)	293 (57)	216 (71)	233 (70)	3,684 (71)	<.0001
Socio-demographics						
Gender						
Male	1,958 (49)	210 (41)	156 (51)	169 (51)	2,493 (48)	
Female	2,060 (51)	302 (59)	148 (49)	163 (49)	2,673 (52)	0.0043
Age Category						
66-69	1,004 (25)	157 (31)	94 (31)	89 (27)	1,344 (26)	
70-74	1,494 (37)	195 (38)	112 (37)	114 (34)	1,915 (37)	
75-79	1,520 (38)	160 (31)	98 (32)	129 (39)	1,907 (37)	0.0089
Marital Status						
Married/ Domestic Partner	2,359 (59)	175 (34)	174 (57)	216 (65)	2,924 (57)	
Not Married	1,659 (41)	337 (66)	130 (43)	116 (35)	2,242 (43)	<.0001
Census Tract Poverty						
0% to <10% poverty	2,017 (50)	80 (16)	80 (26)	157 (47)	2,334 (45)	
10% to <20%	1,105 (28)	121 (24)	93 (31)	66 (20)	1,385 (27)	
20% +	896 (22)	311 (61)	131 (43)	109 (33)	1,447 (28)	<.0001
Residence						
Non-Metropolitan	881 (22)	88 (17)	26 (9)	13 (4)	1,008 (20)	
Metropolitan	3,137 (78)	424 (83)	278 (91)	319 (96)	4,158 (81)	<.0001
Clinical						
Charlson Comorbidity Index						
0	1,910 (48)	179 (35)	129 (42)	156 (47)	2,374 (46)	
1	1,076 (27)	144 (28)	86 (28)	85 (26)	1,391 (27)	
2	499 (12)	73 (14)	34 (11)	48 (15)	654 (13)	
3+	533 (13)	116 (23)	55 (18)	43 (13)	747 (15)	<.0001

Year of Diagnosis						
2007	723 (18)	84 (16)	43 (14)	45 (14)	895 (17)	
2008	678 (17)	89 (17)	48 (16)	54 (16)	869 (17)	
2009	577 (14)	62 (12)	52 (17)	55 (17)	746 (14)	
2010	561 (14)	78 (15)	50 (16)	43 (13)	732 (14)	
2011	505 (13)	62 (12)	36 (12)	44 (13)	647 (13)	
2012	507 (13)	76 (15)	36 (12)	51 (15)	670 (13)	
2013	467 (12)	61 (12)	39 (13)	40 (12)	607 (12)	0.5321
Tumor Location						
Right	2,801 (70)	331 (65)	204 (67)	173 (52)	3,509 (68)	
Left	1,217 (30)	181 (35)	100 (33)	159 (48)	1,657 (32)	<.0001
Tumor Grade						
Well/ Moderately Differentiated	2,727 (68)	377 (74)	217 (71)	243 (73)	3,564 (69)	
Poorly/ Un-differentiated	1,291 (32)	135 (26)	87 (29)	89 (27)	1,602 (31)	0.0114
Length of Stay (categorical)						
< 7 days	2,017 (50)	186 (36)	140 (46)	179 (54)	2,522 (49)	
7-14 days	1,580 (39)	214 (42)	123 (41)	128 (39)	2,045 (40)	
> 14 days	421 (11)	112 (22)	41 (14)	25 (8)	599 (12)	<.0001
Length of Stay (continuous) Median days, IQR	6 (5, 10)	8 (6, 14)	7 (5, 12)	6 (4, 9)	7 (5,10)	

Asian/PI = Asian/Pacific Islander. N (%) = Number (Column Percent). IQR = Interquartile Range.

Figure 2. Adjuvant Chemotherapy Guideline Concordance and Discordance by Race/Ethnicity for Stage III Colon Cancer, SEER-Medicare 2007-2013

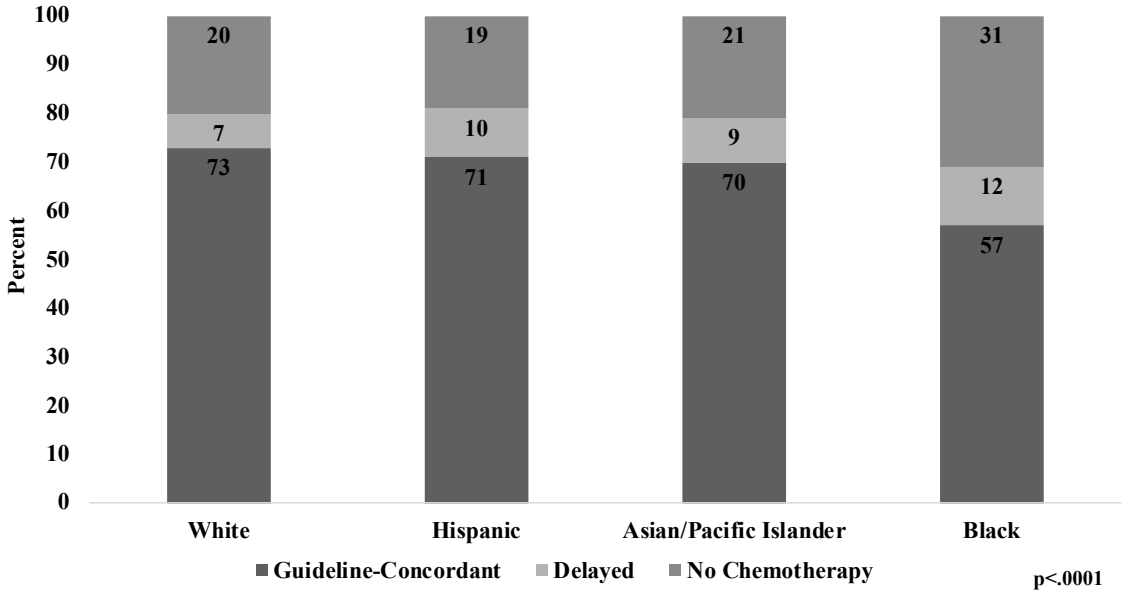


Table 2. Race/Ethnicity and Adjuvant Chemotherapy Guideline Discordance vs. Guideline Concordance for Stage III Colon Cancer, SEER-Medicare 2007-2013 (Multinomial Logistic Regression Model Results)

	Adjuvant Chemotherapy Delayed vs. Received within 4 Months of Diagnosis			**Adjuvant Chemotherapy Omitted vs. Received within 4 Months of Diagnosis**		
	RRR (95% CI) Crude	RRR (95% CI) Sociodemo	RRR (95% CI) Sociodemo + Clinical	RRR (95% CI) Crude	RRR (95% CI) Sociodemo	RRR (95% CI) Sociodemo + Clinical
White	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
Black	2.23 (1.64 to 3.03)*	1.92 (1.38 to 2.66)*	1.69 (1.21 to 2.36)*	1.98 (1.61 to 2.44)*	1.78 (1.42 to 2.22)*	1.42(1.12 to 1.80)*
Hispanic	1.54 (1.03 to 2.30)*	1.39 (0.92 to 2.09)	1.33 (0.87 to 2.01)	0.98 (0.72 to 1.32)	0.98 (0.72 to 1.33)	0.87 (0.63 to 1.21)
Asian/ Pacific Islander	1.38 (0.92 to 2.07)	1.29 (0.86 to 1.95)	1.40 (0.92 to 2.12)	1.09 (0.83 to 1.44)	1.11 (0.84 to 1.48)	1.18 (0.88 to 1.59)

Note: RRR = Relative Risk Ratio. CI = Confidence Interval. * = Statistically Significant. Ref = Reference
Crude = unadjusted model
Sociodemo = Model adjusted for sociodemographic factors
Sociodemo + Clinical = Model adjusted for sociodemographic + clinical factors

CHAPTER 3: (Paper 2) Racial/Ethnic Disparities in Timeliness of Adjuvant Chemotherapy Receipt for Stage III Colon Cancer: Wait Time Disparities before and after Tumor Resection

OVERVIEW

Background

Racial/ethnic disparities in timeliness of care remains an understudied area of research, particularly for colorectal cancer. This research focused on stage III colon cancer, where treatment includes surgical resection of the tumor followed by adjuvant chemotherapy. Delays to initiate chemotherapy are associated with worse patient survival rates. We investigated racial/ethnic disparities in wait times to initiate adjuvant chemotherapy after diagnosis, while breaking down this interval to assess wait time disparities within treatment sub-intervals (before and after tumor resection) to better understand which sub-intervals are likely to contribute to chemotherapy delays.

Methods

Linked Surveillance and Epidemiology and End Results (SEER) registry and Medicare claims data were used. Patients diagnosed with stage III colon cancer during 2007-2013 were included. We examined three outcomes, which were time intervals measured as the number of days from: 1. diagnosis to chemotherapy initiation (overall interval) 2. diagnosis to surgical resection (sub-interval) 3. surgical resection to chemotherapy initiation (sub-interval). The key independent variable was race/ethnicity. Cox proportional hazard regression models adjusting for covariates were run to assess racial/ethnic differences in wait times for each interval.

Results

A hazard ratio < 1 indicates longer wait times to the treatment in each interval. Compared to White patients, all minorities had significantly longer wait times to initiate chemotherapy after diagnosis (the overall interval). Breaking this down into the sub-intervals, Black patients had significantly longer wait times for both sub-intervals:

diagnosis to surgery (HR= 0.882, CI= 0.801-0.973) and surgery to chemotherapy initiation (HR= 0.783, CI= 0.689-0.889). Hispanic patients experienced significantly longer wait times for one sub-interval: diagnosis to surgery (HR= 0.843, CI= 0.749-0.950), whereas Asian/Pacific Islander patients experienced significantly longer wait times for the other sub-interval: surgery to chemotherapy initiation (HR= 0.730, CI= 0.595-0.895). Another important finding is that a large proportion of patients had the same diagnosis and surgery date, majority of which had unplanned surgeries.

Conclusions

This population-based study found racial/ethnic disparities in wait times to initiate chemotherapy after diagnosis, while elucidating treatment sub-intervals where minority patients were likely to experience longer wait times compared to White patients. In addition, unplanned surgeries for this patient population warrant further attention. This study adds to the limited body of research on racial/ethnic disparities in timeliness of colon cancer treatment and identifies specific time periods where interventions could be considered for different racial/ethnic populations.

INTRODUCTION

Racial/ethnic disparities in timeliness of care remains an understudied area of research, particularly for colorectal cancer, which is one of the most commonly diagnosed cancers and a leading cause of cancer death in the U.S. [3]. This research focused on stage III colon cancer, where established treatment includes surgical resection of the tumor followed by adjuvant chemotherapy. Delays to initiate chemotherapy are associated with worse patient survival rates. Relative overall survival decreases by 14% for every 4-week delay after surgery among patients with resected colorectal cancer [1]. To aid in timely chemotherapy receipt, a guideline endorsed by the National Quality Forum (NQF) recommends patients with stage III colon cancer to initiate chemotherapy within 4 months of diagnosis [19].

Early studies reported that Black patients with stage III colon cancer were less likely than White patients to receive adjuvant chemotherapy [11, 12]. However, very little is known about racial/ethnic disparities in delays to initiate chemotherapy despite implications for patient survival. Two studies assessing delays from surgical resection to chemotherapy initiation did not find disparities [36, 44], while findings from a recent study we conducted indicated that Black patients were more likely to initiate chemotherapy beyond 4 months of diagnosis compared to White patients.

The current study built on existing research and investigated racial/ethnic disparities in wait times to initiate adjuvant chemotherapy after diagnosis, while breaking down this interval to assess wait time disparities within treatment sub-intervals (before and after tumor resection) to better understand which sub-intervals are likely to contribute to chemotherapy delays. Disparities in time to treatment in either or both of the sub-

intervals will elucidate areas to address when aiming to reduce disparities in chemotherapy delay.

METHODS

Data Source

We used data sponsored by the National Cancer Institute (NCI) – the linked Surveillance and Epidemiology and End Results (SEER) cancer registry and Medicare claims dataset (2006-2014).

Study Population

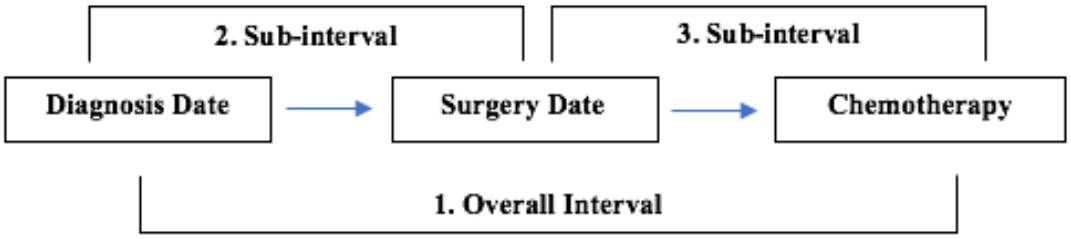
The NQF-endorsed guideline (2007-present) eligibility criteria were used to inform eligibility for this study population [19]. The cohort included persons aged 66-79 with a stage III colon cancer diagnosis between January 1, 2007 and December 31, 2013. Colon cancer diagnoses were identified with ICD-O-3 site codes: C18.0, C18.2-C18.9. Stage IIIs were identified with American Joint Committee on Cancer (AJCC) Stage Group variables from SEER, 6th edition (codes 50-54) and 7th edition (codes 500-542). We further restricted the cohort to those that had a colon resection, identified by ICD-9-CM procedure codes beginning with 45.7, 45.8, and 17.3. Those likely to have complete Medicare fee-for-service (FFS) claims, with both Parts A and B coverage for at least one year after diagnosis or until death were included. FFS A+B claims one year prior to diagnosis were also required to obtain a complete comorbidity profile [55, 56]. Additional standard exclusions consisted of: health maintenance organization (HMO) enrollment, diagnosis after autopsy/death certificate, death within 4 months of diagnosis, any prior cancer diagnoses, any colorectal resection prior to diagnosis or more than 12 months after diagnosis, chemotherapy claims before diagnosis or surgery. After applying

the eligibility criteria, the final study population number was 5,166. See Appendix for selection details.

Dependent Variables

We examined three outcomes, which were time intervals measured as the number of days between two specific dates (Figure 3): 1. diagnosis to chemotherapy initiation (overall interval) 2. diagnosis to surgical resection (sub-interval) 3. surgical resection to chemotherapy initiation (sub-interval).

Figure 3. Three Treatment Time Intervals (Days) for Stage III Colon Cancer



All dates were identified using Medicare sources. The diagnosis date is defined as the earliest claim date containing a colon cancer ICD-9-CM diagnosis code (153.0-153.4, 153.6-153.9). The surgery date is defined as the earliest claim date containing a colon resection ICD-9-CM procedure code. The chemotherapy date is defined as the earliest claim date containing a colon cancer diagnosis code and a chemotherapy code. We used chemotherapy codes similar to other published studies during this time period [57] (see Appendix for list of codes). Persons first receiving chemotherapy more than 12 months after diagnosis were classified as not receiving chemotherapy.

Key Independent Variable

The key independent variable, race/ethnicity, was obtained from SEER sources with the following categories: Non-Hispanic White, Black, Hispanic, and Asian/Pacific

Islander. Very small numbers (<11) Hispanic Black and Hispanic Asian/Pacific Islanders were grouped with their respective race categories.

Covariates

Sociodemographic variables obtained from SEER sources included gender (male, female), age (66-69, 70-74, 75-79), marital status (married/domestic partner or unmarried), census tract poverty (0% to <10% poverty, 10% to <20%, ≥20%), and residence (metropolitan or non-metropolitan) [58]. Clinical variables obtained from SEER sources included year of colon cancer diagnosis (2007-2013), tumor grade (well/moderately differentiated or poorly/undifferentiated/unknown), tumor location (left or right side of colon). Medicare data were used to obtain length of stay (LOS) after surgery (continuous), and to create the Charlson comorbidity index (CCI; 0, 1, 2, or 3+) [55, 56].

Statistical Methods

To assess unadjusted racial/ethnic variations in wait times for each time interval, we examined Kaplan-Meier (K-M) survival curves with Log-rank and Wilcoxon tests and conducted Kruskal-Wallis tests. For full adjustment, we conducted survival analyses (time-to-event) using Cox proportional hazard regression models to assess covariate-adjusted racial/ethnic differences in wait times for each interval. For the two intervals where the event was chemotherapy initiation, LOS was included as a covariate in models, and patients who did not initiate chemotherapy within 12 months of diagnosis or who died before then were censored. For the interval where the event was surgical resection, LOS was not included in the model, and there was no censoring since all patients in the study underwent surgery. We tested for proportional hazards by assessing the significance of an interaction between race/ethnicity and each time interval. This

interaction term was included in final models that indicated a violation of the proportional hazards assumption.

We reported adjusted results using hazard ratios (HRs). In this study, a HR<1 indicates longer wait times to treatment. Additional sensitivity analyses were conducted to ensure that results were not sensitive to analytic decisions, such as excluding those that died within 4 months of diagnosis, using the date of diagnosis from Medicare claims rather than SEER, and including those diagnosed at surgery. All significance tests were two-sided. All data management and analyses were conducted using SAS 9.4 (SAS Institute, Cary NC).

RESULTS

Study characteristics are presented in Table 3. The majority of the study population was White and aged 70 or older. It is important to note that 35% of patients were diagnosed on the same day as their surgical resection (surgery date and diagnosis date were the same); most of these were unplanned surgeries (results not shown).

Important differences in population characteristics across racial/ethnic groups were observed, where a higher percentage of Black patients were living in high poverty census tracts, unmarried, exhibited severe comorbidity, were diagnosed at surgery, and had hospital stays greater than 14 days. Higher percentages of Asian and Hispanic patients lived in metropolitan areas.

Figures 4-6 are K-M survival curves where "survival probability" represents the probability of remaining un-treated over time (probability of waiting for surgery or to start adjuvant chemotherapy). Since the K-M curves reflect wait times to treatment, longer "survival" or longer time to each event is not the desired outcome for this study. Log-rank and Wilcoxon tests showed significant differences between racial/ethnic K-M

curves for all three intervals. For the diagnosis to chemotherapy interval (Figure 4) and the surgery to chemotherapy sub-interval (Figure 6), the Black patient curves had separated early on and clearly stood apart, indicating longer wait times to chemotherapy throughout the study period. Although less noticeable, the Hispanic and Asian/Pacific Islander K-M curves for those intervals also indicated longer wait times than White patients. An important finding is that Asian and Hispanic patients had consistently longer wait times to initiate chemotherapy during the first 4 months of diagnosis (Figure 4). Although significant, the K-M curves for the diagnosis to surgery sub-interval (Figure 5) were less distinguishable between the racial/ethnic groups.

Table 4 presents unadjusted median number of days to treatment for each interval by race/ethnicity. For all three intervals, the median time to treatment was longer for minorities compared to White patients. The exception was that Black patients had the shortest median days between diagnosis and surgery (8 days; IQR: 0, 28). This was influenced by the large proportion of Black patients that were diagnosed on the same day as their surgery so that the difference between diagnosis and surgery dates was zero days. Sensitivity analyses excluding all patients diagnosed on their surgery date revealed that Black patients had the longest wait time between diagnosis and surgery (26 days; IQR: 14, 40). To avoid masking this disparity, Table 4 is stratified by results that 1. include those diagnosed at surgery, 2. exclude those diagnosed at surgery, and 3. only include those diagnosed at surgery.

Table 5 presents the adjusted Cox proportional hazard regression estimates. The proportional hazards test indicated violation of the assumption for two intervals: diagnosis to chemotherapy ($p=0.0006$) and surgery to chemotherapy ($p=0.0430$), though these were small and borderline significant violations. An interaction term between

race/ethnicity and the time intervals was included in the final models to account for the violations.

Adjusted regression results showed that all minorities had significantly longer wait times between diagnosis and chemotherapy initiation (overall interval) compared to White patients, as indicated by hazard ratios < 1. Breaking this down into the sub-intervals, Black patients had significantly longer wait times for both sub-intervals: diagnosis to surgery (HR= 0.882, CI= 0.801-0.973) and surgery to chemotherapy initiation (HR= 0.783, CI= 0.689-0.889). Hispanic patients experienced significantly longer wait times for one sub-interval: diagnosis to surgery (HR= 0.843, CI= 0.749-0.950), whereas Asian/Pacific Islander patients experienced significantly longer wait times for the other sub-interval: surgery to chemotherapy initiation (HR= 0.730, CI= 0.595-0.895).

Sensitivity analyses excluding those diagnosed at surgery showed similar direction and significance for all the HRs, with slightly lower effect size, indicating even longer wait times to each event. The largest changes from the sensitivity analyses were: the Black diagnosis to surgery HR went from 0.882 (0.801-0.973) to 0.771 (0.680-0.875) and the Hispanic surgery to chemotherapy HR became statistically significant after excluding those diagnosed at surgery.

DISCUSSION

Delays to initiate adjuvant chemotherapy for stage III colon cancer has implications for patient survival [1]. A guideline recommends patients to initiate adjuvant chemotherapy within 4 months of diagnosis. In a previous study, we found that Black patients were more likely to initiate chemotherapy after 4 months of diagnosis compared to White patients. In the current study, we further elucidated potential areas of

intervention to address the Black-White disparity in delayed chemotherapy initiation. Results indicated that the overall Black-White disparity can be attributed to significantly longer wait times in two sub-intervals (diagnosis to surgery and surgery to chemotherapy).

In our previous study, we found that Asian and Hispanic patients were likely to initiate chemotherapy within 4 months of diagnosis as recommended by the guideline. In the current study, we demonstrated that Asian and Hispanic patients still had longer wait times to initiate chemotherapy during those 4 months compared to White patients. Given that delaying chemotherapy by a matter of weeks significantly reduces survival, our findings indicate opportunity for improvement even among patient groups that are receiving treatment within the guideline parameters. The overall Hispanic-White disparity can be attributed to one sub-interval (diagnosis to surgery) and the overall Asian-White disparity can be attributed to longer wait times in the other sub-interval (surgery to chemotherapy).

Part of these findings are consistent with other studies that have found Black and Hispanic disparities in delayed time to surgical resection [13, 40, 41]. Our other findings are different from two previous studies that did not find disparities in wait times between surgery and chemotherapy [36, 44]. It is possible this is due to differences in the study populations and methods used in these studies.

It is important to note that our analyses included those diagnosed on the same day as surgery (a zero-day difference between the diagnosis date and the surgery date), which disproportionately affected Black patients. The majority of these cases had unplanned surgeries. Black patients have previously been shown to have a higher rate of unplanned colon cancer resections [37-39], which are associated with worse disease-free survival

[38]. Being diagnosed on the same day as a colon resection is an indication of delayed screening and diagnosis, where disparities have also been found [23-25]. Studies that assess timeliness of surgery for colon cancer handle these cases by excluding them from the study [40, 41]; however we kept these cases in our analyses since the main event of interest for the present study was adjuvant chemotherapy initiation for those that had a resection. When assessing wait time differences from diagnosis to surgery, it is important to consider the zeros so that racial disparities in both unplanned surgeries and longer wait times for the planned surgeries are not masked. Evaluation of the NQF-endorsed guideline for initiating chemotherapy may also need to take this into consideration. Hospitals should also consider monitoring the rate of planned versus unplanned colon cancer resections given the high rate of unplanned surgeries and variation by race/ethnicity found in this study.

This study has limitations that must be acknowledged. We cannot determine that a patient's race/ethnicity is the cause of differential wait times to treatment, but we can determine that race/ethnicity is associated with differences in wait times. As with most observational studies, we could not control for all possible patient, provider, and structural confounders. Additionally, findings may not be generalizable to younger populations.

Despite limitations, this study has considerable strengths. We used NCI-sponsored linked SEER-Medicare data, which are population-based data sources covering approximately 28% of the U.S. population (SEER) and the majority of elderly Americans (Medicare). This study also included Hispanic and Asian/Pacific Islander patients, which are traditionally understudied populations in health services research. In addition, we applied survival analyses or time-to-event models, which are typically used in studies

where the event is death rather than treatment. This allowed us to estimate differences in wait times to treatment while controlling for confounders, and censoring those who did not receive adjuvant chemotherapy by the end of the study period. We also note important findings of racial disparities in diagnoses occurring on the day of resection, which warrant further attention.

Racial/ethnic equity in timeliness of adjuvant chemotherapy receipt remains an understudied area of research, despite implications for patient survival. In this population-based study, we found that compared to White patients, all minority patients had significantly longer wait times between diagnosis and adjuvant chemotherapy initiation. Two sub-intervals indicated further nuance for each minority group. Barriers should be assessed in these intervals with consideration that each has different health care providers in varied settings. This study adds to the limited body of research on racial/ethnic variation in colon cancer treatment timing, and can inform interventions to reduce disparities in timeliness of cancer care.

Table 3. Sociodemographic and Clinical Characteristics of Patients with Stage III Colon Cancer by Race/Ethnicity, Ages 66-79, SEER-Medicare 2007-2013 Diagnoses

	White N=4018 78%	**Black** N=512 10%	**Hispanic** N=304 6%	**Asian/PI** N=332 6%	**Total** N=5166 100%	
	N (%)	N (%)	N (%)	N (%)	N (%)	P-value
Socio-demographic						
Gender						
Male	1,958 (49)	210 (41)	156 (51)	169 (51)	2,493 (48)	
Female	2,060 (51)	302 (59)	148 (49)	163 (49)	2,673 (52)	0.0043
Age Category						
66-69	1,004 (25)	157 (31)	94 (31)	89 (27)	1,344 (26)	
70-74	1,494 (37)	195 (38)	112 (37)	114 (34)	1,915 (37)	
75-79	1,520 (38)	160 (31)	98 (32)	129 (39)	1,907 (37)	0.0089
Marital Status						
Married/ Domestic Partner	2,359 (59)	175 (34)	174 (57)	216 (65)	2,924 (57)	
Not Married	1,659 (41)	337 (66)	130 (43)	116 (35)	2,242 (43)	<.0001
Census Tract Poverty						
0% to <10% poverty	2,017 (50)	80 (16)	80 (26)	157 (47)	2,334 (45)	
10% to <20%	1,105 (28)	121 (24)	93 (31)	66 (20)	1,385 (27)	
20% +	896 (22)	311 (61)	131 (43)	109 (33)	1,447 (28)	<.0001
Residence						
Non-Metropolitan	881 (22)	88 (17)	26 (9)	13 (4)	1,008 (20)	
Metropolitan	3,137 (78)	424 (83)	278 (91)	319 (96)	4,158 (81)	<.0001
Clinical						
Charlson Comorbidity Index						
0	1,910 (48)	179 (35)	129 (42)	156 (47)	2,374 (46)	
1	1,076 (27)	144 (28)	86 (28)	85 (26)	1,391 (27)	
2	499 (12)	73 (14)	34 (11)	48 (15)	654 (13)	
3+	533 (13)	116 (23)	55 (18)	43 (13)	747 (15)	<.0001
Year of Diagnosis						
2007	723 (18)	84 (16)	43 (14)	45 (14)	895 (17)	
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2009	577 (14)	62 (12)	52 (17)	55 (17)	746 (14)	

2010	561 (14)	78 (15)	50 (16)	43 (13)	732 (14)	
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2012	507 (13)	76 (15)	36 (12)	51 (15)	670 (13)	
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Tumor Location						
Right	2,801 (70)	331 (65)	204 (67)	173 (52)	3,509 (68)	
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Tumor Grade						
Well/ Moderately Differentiated	2,727 (68)	377 (74)	217 (71)	243 (73)	3,564 (69)	
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Length of Stay (categorical)						
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7-14 days	1,580 (39)	214 (42)	123 (41)	128 (39)	2,045 (40)	
> 14 days	421 (11)	112 (22)	41 (14)	25 (8)	599 (12)	<.0001
Length of Stay (continuous) Median days, IQR	6 (5, 10)	8 (6, 14)	7 (5, 12)	6 (4, 9)	7 (5,10)	
Diagnosed at Surgery	1,375 (34)	212 (41)	97 (32)	105 (32)	1,789 (35)	0.0046

Asian/PI = Asian/ Pacific Islander. N (%) = Number (Column Percent). IQR = Interquartile Range.

Table 4. Median Time to Treatment (Days) for Patients with Stage III Colon Cancer by Race/Ethnicity, Ages 66-79, SEER-Medicare 2007-2013 Diagnoses

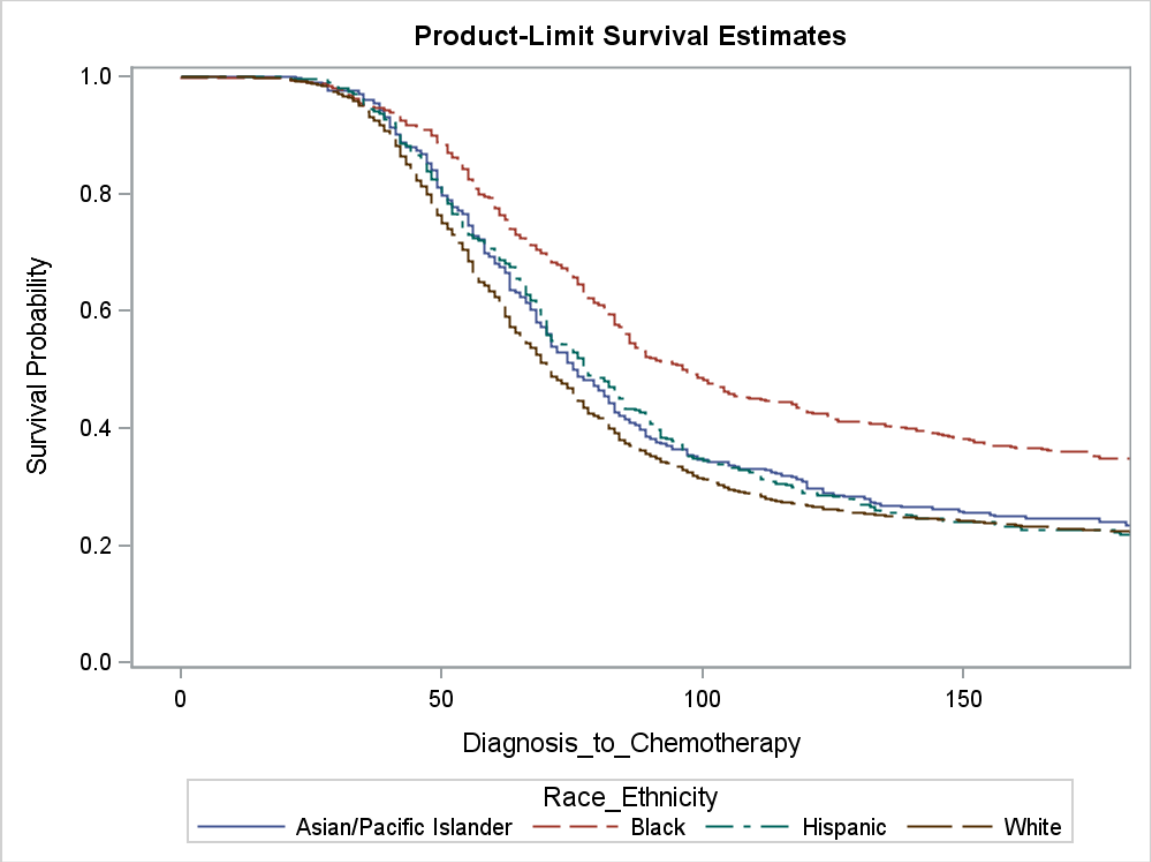
	Including diagnosed at surgery			**Excluding diagnosed at surgery**			**Only diagnosed at surgery**	
	Dx to Chemo	Dx to Sx	Sx to Chemo	Dx to Chemo	Dx to Sx	Sx to Chemo	Dx to Sx	Sx/Dx to Chemo
Overall	63 [48, 84]	11 [0, 24]	48 [38, 64]	69 [54, 89]	20 [11, 31]	46 [36, 61]	0	52 [41, 72]
White	62 [47, 82]	10 [0, 23]	47 [37, 63]	66 [52, 85]	19 [11, 29]	45 [35, 59]	0	52 [41, 71]
Black	76 [55, 100]	8 [0, 28]	54 [41, 76]	82 [62, 106]	26 [14, 40]	51 [39, 69]	0	60 [45, 83]
Hispanic	69 [51, 92]	14 [0, 30]	50 [39, 68]	77 [61, 98]	23 [14, 40]	49 [37, 66]	0	52 [42, 68]
Asian/PI	68 [50, 88]	13 [0, 26]	50 [40, 67]	74 [58, 93]	20 [12, 34]	50 [38, 67]	0	50 [41, 66]
	p <.0001	p =0.014	p<.0001	p<.0001	p<.0001	p<.0001	0	p=0.035

Median days [IQR], Kruskal-Wallis Test.

Note: IQR=Interquartile Range. Dx=Diagnosis Date. Sx=Surgery Date. Chemo=Adjuvant Chemotherapy Initiation Date.
Asian/PI = Asian/ Pacific Islander.

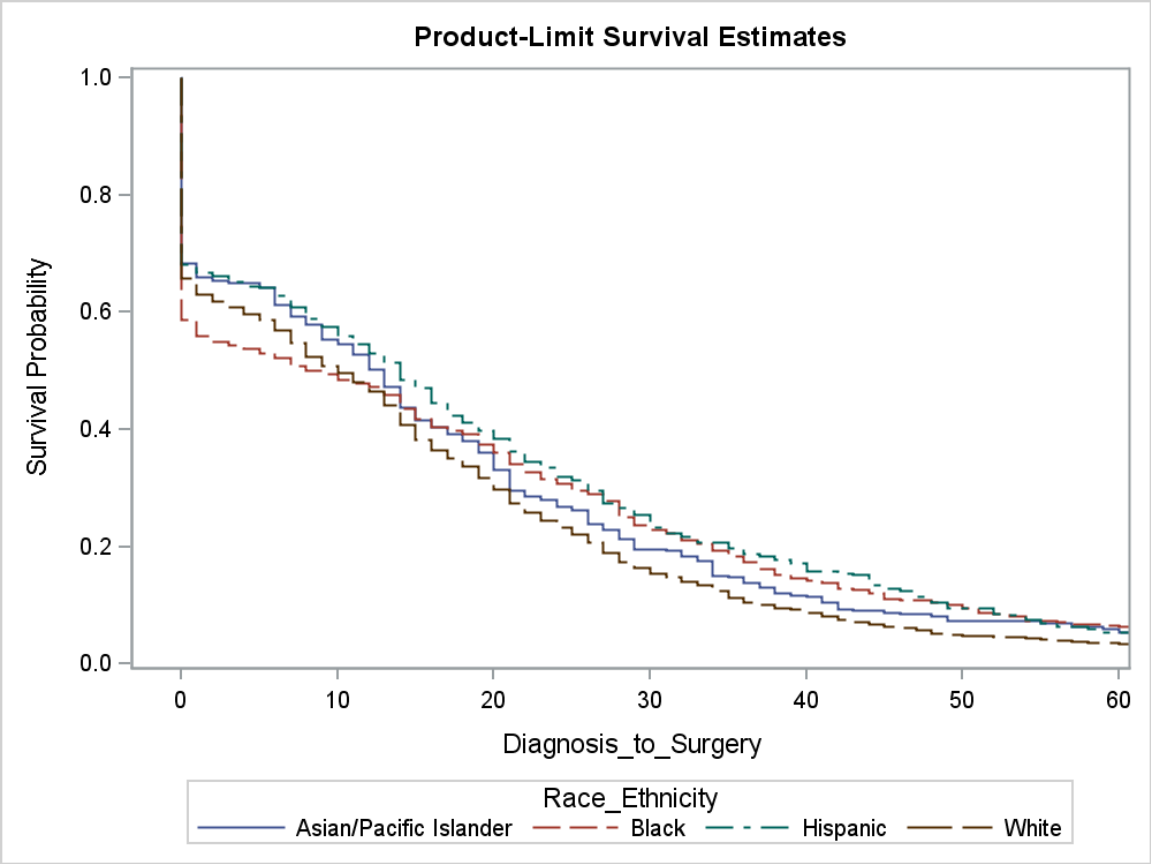
Kaplan-Meier Survival Curves

Figure 4. Probability of Waiting to Initiate Adjuvant Chemotherapy after Diagnosis Over Time (Days) by Race/Ethnicity



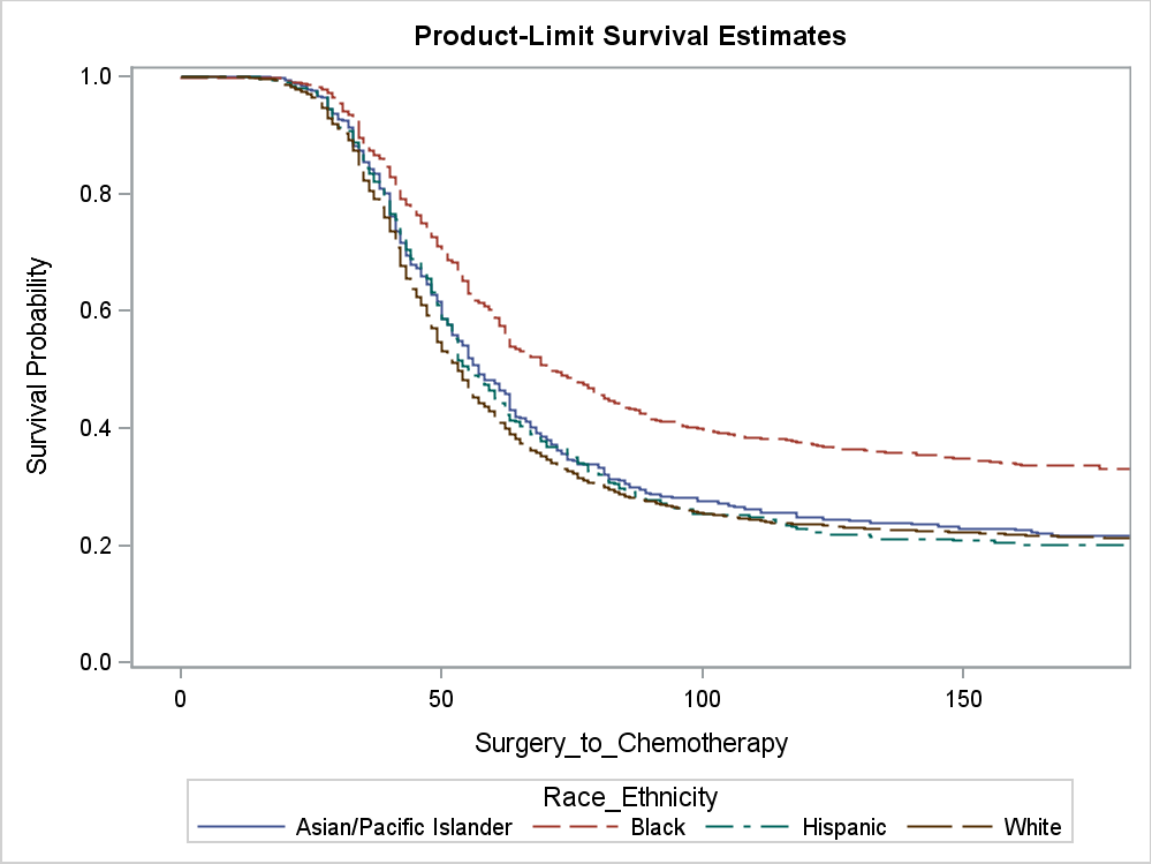
Tests of equality over strata: Log-rank ($p<0.0001$) and Wilcoxon ($p<0.0001$)

Figure 5. Probability of Waiting for Surgical Resection after Diagnosis Over Time (Days) by Race/Ethnicity



Tests of equality over strata: Log-rank ($p<0.0001$) and Wilcoxon ($p=0.0171$)

Figure 6. Probability of Waiting to Initiate Adjuvant Chemotherapy after Surgical Resection Over Time (Days) by Race/Ethnicity



Tests of equality over strata: Log-rank ($p<0.0001$) and Wilcoxon ($p<0.0001$)

Table 5. Race/Ethnicity and Wait Times to Treatment for Stage III Colon Cancer, Ages 66-79, SEER-Medicare 2007-2013 (Cox Proportional Hazard Regression Model Results)

	Diagnosis to Chemotherapy	**Diagnosis to Surgery**	**Surgery to Chemotherapy**
	Adjusted HR (95% CI)	Adjusted HR (95% CI)	Adjusted HR (95% CI)
White	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Black	0.713 (0.627-0.811)*	0.882 (0.801-0.973)*	0.781 (0.688-0.887)*
Hispanic	0.788 (0.663-0.936)*	0.843 (0.749-0.950)*	0.897 (0.760-1.060)
Asian/PI	0.649 (0.522-0.807)*	0.939 (0.838-1.053)	0.729 (0.594-0.894)*

HR=Hazard Ratio. HR < 1 indicates longer wait time to treatment.
CI=Confidence Interval.
* = statistically significant.
All models are fully adjusted for sociodemographic and clinical characteristics.
Asian/PI = Asian/ Pacific Islander.

CHAPTER 4: (Paper 3) Timeliness of Adjuvant Chemotherapy Receipt for Stage III Colon Cancer following a Guideline Change and Racial Differences in Trends Over Time

OVERVIEW

Background

There is limited research on the effectiveness of guidelines to change practice. A guideline endorsed by the National Quality Forum (NQF) in 2007 recommends adjuvant chemotherapy within four months of stage III colon cancer diagnosis. Compared to prior guidelines, the inclusion of a timeframe for initiating chemotherapy is important since the timeliness of chemotherapy receipt has implications for patient survival. The present study aimed to examine patterns of timely chemotherapy receipt over a 10-year period, while assessing whether rates improved after the initial guideline endorsement in 2007. Due to known racial disparities in adjuvant chemotherapy receipt, we also examined changes in trends over time by race.

Methods

The linked Surveillance and Epidemiology and End Results (SEER) cancer registry and Medicare claims data were used. Patients diagnosed with stage III colon cancer during 2004-2013 were included. Using an interrupted time series design (ITS), we estimated changes between pre- and post- guideline periods in the proportion of patients receiving chemotherapy within 4 months of diagnosis, and whether any changes differed by race.

Results

This study found rates of timely chemotherapy receipt remained stable over a recent 10-year period, and did not change (neither immediately nor as part of a trend) from pre- to post- guideline years. Black and White population rates were stable over time, with Black rates remaining consistently lower than White rates.

Conclusions

Research on incorporating equity into guideline measurement and recommendations for equity-focused guideline implementation strategies are needed to reduce disparities in receipt of timely and standard cancer treatment.

INTRODUCTION

Evidence-based clinical practice guidelines or quality measures are developed to promote standardized, high-quality health care. These guidelines play an important role by synthesizing available evidence and providing up-to-date recommendations to health care providers. Despite the wide use of guidelines in the past two decades, studies on the effectiveness of guidelines to standardize practice, including reducing disparities, are limited and mixed [67-70]. An understudied research area is the impact of guidelines on treatment practices for colorectal cancer, despite it being one of the most commonly diagnosed cancers and causes of cancer death in the U.S. [3].

A National Institutes of Health (NIH) Consensus Statement in 1990 recommended adjuvant chemotherapy after surgical resection of stage III colon cancer due to strong evidence that chemotherapy decreases cancer recurrence and improves survival [5]. National guidelines were created following the recommendation, and adjuvant chemotherapy treatment rates have increased over time [7-10]. However, racial disparities in chemotherapy receipt persisted in the following decade [7, 9, 11, 12, 46], which was seen as a partial explanation of Black-White survival differences for stage III colon cancer [30].

The most up-to-date guideline, which emphasizes timely adjuvant chemotherapy receipt (within 4 months of diagnosis) rather than simply receipt, was endorsed by the National Quality Forum (NQF) from 2007-present [19]. Compared to previous guidelines, this inclusion of a timeframe is important since the timeliness of adjuvant chemotherapy initiation is strongly linked to improved survival rates [1]. To date, there has been no examination of whether practice variations changed over time or across racial groups in response to the NQF-endorsed guideline. The present study aimed to

examine patterns of timely chemotherapy receipt over a 10-year period, while assessing whether rates improved after the initial guideline endorsement in 2007. Due to known disparities in adjuvant chemotherapy receipt and colon cancer survival, we also sought to examine whether the guideline change differently impacted racial groups.

METHODS

The objective of this study was to estimate the causal effects of a guideline that recommends initiating chemotherapy within 4 months of stage III colon cancer diagnosis. We used an interrupted time series design (ITS) [67-69, 71], which is a quasi-experimental research design used when the intervention of interest was not randomized. An advantage of this design is that effects of the intervention can be distinguished from secular trends [72]. Using ITS, we estimated changes between pre- and post- guideline periods in the proportion of patients receiving chemotherapy within 4 months of diagnosis, and whether any changes differed by race.

Data Source

We used data sponsored by the National Cancer Institute (NCI) – the linked Surveillance and Epidemiology and End Results (SEER) cancer registry and Medicare claims dataset (2003-2014).

Study Population

The NQF-endorsed guideline (2007-present) eligibility criteria were used to inform eligibility for this study population [19]. The cohort included persons aged 66-79, who were diagnosed with stage III colon cancer between January 1, 2004 and December 31, 2013. Colon cancer diagnoses were identified with ICD-O-3 site codes: C18.0, C18.2-C18.9. Stage IIIs were identified with American Joint Committee on Cancer (AJCC) Stage Group variables from SEER, 6th edition (codes 50-54) and 7th edition

(codes 500-542). We further restricted the cohort to those that had a colon resection, identified by ICD-9-CM procedure codes beginning with 45.7, 45.8, and 17.3. Those likely to have complete Medicare fee-for-service (FFS) claims, with both Parts A and B coverage for at least one year after diagnosis or until death were included. FFS A+B claims one year prior to diagnosis were also required to obtain a complete comorbidity profile [55, 56]. Additional standard exclusions consisted of: health maintenance organization (HMO) enrollment, diagnosis after autopsy/death certificate, death within 4 months of diagnosis, any prior cancer diagnoses, any colorectal resection prior to diagnosis or more than 12 months after diagnosis, chemotherapy claims before diagnosis or surgery. After applying the eligibility criteria, the final study population number was 8,041. See Appendix for selection details.

Primary Outcome

In an ITS analysis, changes in population rates of an outcome are estimated between different time periods. The rows in the dataset are sequential time periods rather than individual patients. In this study, each row corresponded to a quarter during the study period (e.g. quarter 1, 2004; quarter 2, 2004, etc.). The primary outcome was the proportion of patients diagnosed within a quarter who received adjuvant chemotherapy within 4 months of their diagnosis (timely receipt). We used patient-level data of timely chemotherapy receipt to create the ITS dataset and calculate the quarterly proportions.

Diagnosis and chemotherapy dates were identified using Medicare sources. The diagnosis date is defined as the earliest claim date containing a colon cancer ICD-9-CM diagnosis code (153.0-153.4, 153.6-153.9). The chemotherapy date is defined as the earliest claim date containing a colon cancer diagnosis code and a chemotherapy code. We used chemotherapy codes similar to other published studies during this time period

[57] (see Appendix for list of codes). Persons first receiving chemotherapy more than 12 months after diagnosis were classified as not receiving chemotherapy.

Independent Variables

An ITS analysis has three variable specifications for time: 1. a variable representing the secular trend with 2004-2013 quarters numbered sequentially (1-40), 2. a binary variable for pre- and post- guideline periods where 0 is the time period between January 01, 2004 – February 27, 2007 (pre-guideline), and 1 is the time period between February 28, 2007 – December 31, 2013 (post-guideline), and 3. a variable representing the post-guideline trend with post-guideline quarters numbered sequentially (1-28) and pre-guideline quarters numbered 0.

Patient Characteristics

Sociodemographic variables obtained from SEER sources included gender (male, female), age (66-69, 70-74, 75-79), marital status (married/domestic partner or unmarried), census tract poverty (0% to <10% poverty, 10% to <20%, ≥20%), and residence (metropolitan or non-metropolitan) [58]. Clinical variables obtained from SEER sources included year of colon cancer diagnosis (2007-2013), tumor grade (well/moderately differentiated or poorly/undifferentiated/unknown), tumor location (left or right side of colon). Medicare data were used to obtain length of stay (LOS) after surgery (continuous), and to create the Charlson comorbidity index (CCI; 0, 1, 2, or 3+) [55, 56].

Statistical Methods

We began by describing the study population with sociodemographic and clinical characteristics. Significant differences in population characteristics between the pre– and post- guideline periods were assessed with chi-square tests. Unadjusted rates of timely

chemotherapy receipt before and after the guideline were assessed with chi-square tests. Unadjusted racial differences in the pre- and post- guideline rates were also assessed with chi-square tests.

We then conducted an ITS analysis to assess the impact of the guideline on subsequent timely chemotherapy rates. With this design, the guideline's immediate effect (with binary time variable) and sustained effect (with post-guideline trend variable) on timely chemotherapy receipt were assessed while adjusting for secular trends.

After visual inspection of the quarterly trend from 2004-2013, we computed the Durbin-Watson statistic for autocorrelation to test the assumption that the error terms are independent. This is important with time series analyses since observations that are closer together might be correlated. Model fit was assessed with diagnostic plots (i.e. studentized residual plot). Finally, we ran an ITS regression model, and included the three independent time variables. To estimate these coefficients with sufficient power, a minimum of 8 time points were required for each segment (8 each for pre- and post-guideline periods) [72]. There were 12 pre-guideline and 28 post-guideline quarters. In ITS, since the outcomes are population rates, not individual rates, individual-level variables were not included in the model [72]. All significance tests were two-sided. All data management and analyses were conducted using SAS 9.4 (SAS Institute, Cary NC).

RESULTS

Table 6 presents the sociodemographic and clinical characteristics of the study population for both the pre- and post- guideline periods. Most were White, aged 70 or older, exhibited low comorbidity, lived in a metropolitan area, and resided in a low poverty census tract (i.e., 0 to 20% poverty). Study characteristics between the pre- and post- guideline periods were generally similar with the exception that the post-guideline

period had a significantly higher percentage of patients in the highest poverty census tracts compared to the pre-guideline period.

In both pre- and post- guideline periods, 71% of the patient population received timely adjuvant chemotherapy (Table 6). Black patients had significantly lower rates of timely chemotherapy receipt than White patients in both time periods. There was no graphical evidence of this gap narrowing, or general rates of timely chemotherapy changing over time (Figure 7).

For the ITS analysis, the Durbin-Watson test, including tests for higher orders, indicated no autocorrelation. Regression results presented in Table 7 indicated that the secular trend was not statistically significant (p=0.2266), indicating that trends of timely chemotherapy receipt were not changing significantly from quarter to quarter. The binary coefficient was quite small and not statistically significant (p=0.3222), indicating no changes in timely chemotherapy rates immediately following the guideline. The post-guideline coefficient was also small and not statistically significant (p=0.1948), indicating the slopes did not change significantly between the pre- and post-guideline years. The ITS analysis was not stratified by race/ethnicity due to smaller sample sizes in the quarterly time points for minority groups.

DISCUSSION

A clinical practice guideline for stage III colon cancer recommends initiating chemotherapy within 4 months of diagnosis. The subsequent effects of this guideline have not been previously investigated, and contemporarily analysis of timely chemotherapy rates in the advanced colon cancer population are limited. In addition, research on racial disparities in timely chemotherapy trends are scarce.

The present study found rates of timely chemotherapy receipt remained stable over a recent 10-year period, and did not change (neither immediately nor as part of a trend) from pre- to post-guideline years. Given that timely chemotherapy receipt has implications for patient survival, our results suggest there may be room for overall improvement; however, this particular guideline does not list an expected performance rate, and is not expected to be 100%.

There is evidence that the strategy for guideline rollout may impact the effectiveness of guidelines. Specific recommendations for how to implement the guideline may be useful to improve guideline-adherence and standardize care, especially since implementation can entail multiple health care providers and settings. Gagliardi suggested that implementation planning occur during the guideline development process, with tools and strategies published concurrently with the guideline [73]. There are many considerations for implementation planning, tools, and strategies [73-78], although higher quality research at multiple levels is needed to improve our understanding of the most effective options [66, 73, 77, 78]. Such research will be important to clarify the intended clinical audience of the guideline [79], and to improve the timely transition of patients between treatment settings (e.g. surgical facility, chemotherapy settings) [19].

Guidelines also have the opportunity to reduce racial disparities; however our results indicated that disparities persisted over time. Black and White rates were stable over time, with Black rates remaining consistently lower than White rates. Several have commented that guidelines have the opportunity to reduce disparities in recommended care by explicitly incorporating equity into implementation of the guideline [80-85]. To address disparities, guideline users should be informed of the specific nature of disparities, provided with recommendations on how to fairly assess disparities for public

reporting, and given recommendations for implementing specific equity-focused interventions at multiple levels [64, 80, 86-90]. Assessment and reporting of disparities is particularly important before discontinuing public reporting of measures that had "topped out" for the overall patient population, as was the case for this guideline in the Prospective Payment System (PPS)-Exempt Cancer Hospital Quality Reporting (PCHQR) Program [91]. Organizations could otherwise miss important patterns of low or delayed treatment rates in their smaller, disadvantaged patient populations, and risk lowering standards for these populations.

The wide use of guidelines in the past two decades has been critical to systematically examine and quantify the quality of health care in the U.S.; however, larger efforts are needed to reduce quality of care disparities. Although the guideline examined did not reduce disparities, future directions outlined by NQF for systematically addressing health care disparities are promising. In a recent comprehensive report, NQF outlined a roadmap for using performance measures to incentivize achieving equity through accountability [80]. However, the report acknowledges, "performance measurement in healthcare, while critical to monitoring and reducing disparities, is one of many tools needed to eliminate health disparities […] the causes of disparities represent complex interactions among institutional, historical, and sociopolitical factors that can only be fully addressed through a variety of mechanisms" [80].

This study has some limitations that must be acknowledged. A suitable control group was unavailable to strengthen the study design since groups that were not exposed to the guideline could not be ascertained, although this would be more of a limitation if our results indicated the guideline had an effect on the outcome. Also, in order to obtain the recommended minimum number of 8 time points for both before and after the

guideline [72], we used quarterly time points. This also meant we could not conduct a stratified ITS analysis by race/ethnicity due to smaller sample sizes for minority groups within each quarter. Additionally, this study may not be generalizable to younger populations. However, the target population for this measure is the elderly below age 80.

Despite limitations, this study has important strengths. We used NCI-sponsored linked SEER-Medicare data, which are population-based data sources covering approximately 28% of the U.S. population (SEER) and the majority of elderly Americans (Medicare). We used a quasi-experimental design to assess the causal effects of a guideline that has not been studied for its effects on timely chemotherapy receipt. Threats to validity were considered, including history (any competing interventions that occurred at the same time since we can only control for secular trend, not competing interventions), changes in instrumentation (changes in the way the outcome is measured, such as changes in chemotherapy codes over time), and selection bias (i.e. if Medicare population characteristics changed at the same time as the guideline).

In conclusion, this population-based study found that trends in timely chemotherapy receipt remained stable over a 10-year period, and did not change after the current guideline went into effect. Black patient population rates remained consistently lower than White rates. Addressing this gap is important since racial disparity in chemotherapy receipt is associated with some of the survival disparity among stage III colon cancer patients. In addition, timeliness of chemotherapy receipt also has implications for patient survival. Research on incorporating equity into guideline measurement and recommendations for equity-focused guideline implementation strategies are needed to reduce disparities in receipt of timely and standard cancer treatment.

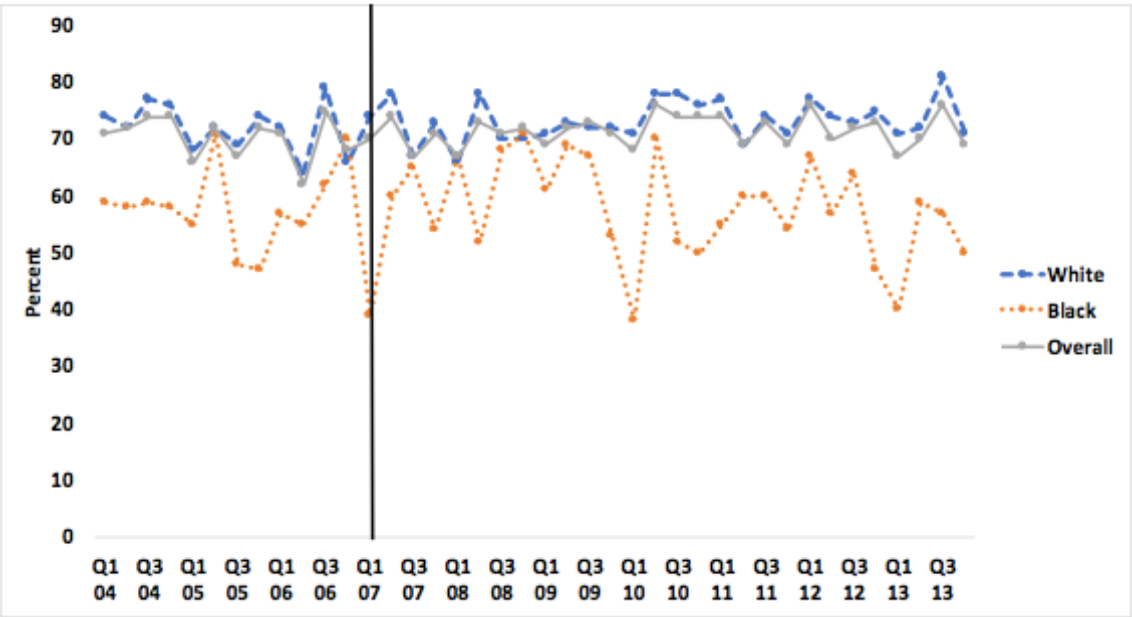
Table 6. Sociodemographic and Clinical Characteristics of Patients with Stage III Colon Cancer, Ages 66-79, SEER-Medicare 2004-2013 Diagnoses

	Pre-Guideline (1/2004-2/2007)		Post-Guideline (3/2007-12/2013)		Total (2004-2013)		
	N=3030 (37.68%)		N=5011 (62.32%)		N=8041 (100%)		
	N	%	N	%	N	%	P-value
Adjuvant Chemotherapy Receipt within 4 Months of Diagnosis	2138	71	3577	71	5715	71	0.430
Race/Ethnicity							
White	2,377	78	3,896	78	6,273	78	
Black	321	11	496	10	817	10	
Hispanic	163	5	297	6	460	6	
Asian/PI	169	6	322	6	491	6	0.237
Gender							
Male	1,380	46	2,422	48	3,802	47	
Female	1,650	55	2,589	52	4,239	53	0.015
Age							
66-69	797	26	1,293	26	2,090	26	
70-74	1,061	35	1,866	37	2,927	36	
75-79	1,172	39	1,852	37	3,024	38	0.120
Marital Status							
Married/Domestic Partner	1,779	59	2,828	56	4,607	57	
Not Married	1,251	41	2,183	44	3,434	43	0.045
Census Tract Poverty							
0% to <10% poverty	1,596	53	2,253	45	3,849	48	
10% to <20%	846	28	1,349	27	2,195	27	
20% +	588	19	1,409	28	1,997	25	<.0001
Residence							
Non-Metropolitan	564	19	976	20	1,540	19	
Metropolitan	2,466	81	4,035	81	6,501	81	0.340
Charlson Comorbidity Index							
0	1,503	50	2,297	46	3,800	47	
1	818	27	1,348	27	2,166	27	
2	387	13	640	13	1,027	13	
3+	322	11	726	15	1,048	13	<.0001
Tumor Location							
Right	2,035	67	3,402	68	5,437	68	

Left	995	33	1,609	32	2,604	32	0.498
Tumor Grade							
Well/Moderately Differentiated	2,070	68	3,457	69	5,527	69	
Poorly/Un-differentiated	960	32	1,554	31	2,514	31	0.529
Length of Stay (categorical)							
< 7 days	1,197	40	2,459	49	3,656	46	
7-14 days	1,429	47	1,975	39	3,404	42	
> 14 days	404	13	577	12	981	12	<.0001
Length of Stay (continuous) Median days, IQR	7 (5,11)		7 (5,10)		7(5,10)		<.0001

Asian/PI = Asian/ Pacific Islander. IQR = Interquartile Range.

Figure 7. Unadjusted Trends of Adjuvant Chemotherapy Receipt within 4 Months of Diagnosis for Patients with Stage III Colon Cancer by Race, SEER-Medicare 2004-2013



Note: The guideline was endorsed by the NQF in quarter 1, 2007.

Table 7. Changes in Timely Chemotherapy Receipt before and after the 2007 Guideline for Stage III Colon Cancer, SEER-Medicare Quarterly Time Periods from 2004-2013 (Interrupted Times Series Results)

	Estimate	P-value
Intercept	0.7242	<0.0001
Secular Trend	-0.002893	0.2266
Pre/Post Immediate Change	0.0195	0.3222
Post-Guideline Trend Change	0.003274	0.1948

CHAPTER 5: CONCLUSION

This dissertation focused on an understudied area in health care quality: racial/ethnic disparities in timeliness of care. Particularly lacking is research on disparities in receiving timely treatment for colon cancer. To address this knowledge gap, three studies were conducted, which focused on an NQF-endorsed guideline that recommends patients with stage III colon cancer to receive surgery and adjuvant chemotherapy within 4 months of diagnosis.

SUMMARY OF FINDINGS

In the first study, racial/ethnic disparities in chemotherapy receipt and delay were assessed. This study is the first that we know of that assessed disparities in concordance with the current NQF-endorsed guideline. It is also the first study that disaggregated guideline discordance to distinguish between disparities in omitted chemotherapy versus delayed chemotherapy. In line with other research, our results showed that Black patients were less likely to receive chemotherapy than were White patients. The new finding from this study is that Black patients were also more likely to have delayed chemotherapy initiation (beyond 4 months of diagnosis).

In the second study, we further assessed racial/ethnic disparities in wait times for three treatment intervals, measured as the number of days from: 1. diagnosis to chemotherapy initiation (overall interval), 2. diagnosis to surgical resection (sub-interval), 3. surgical resection to chemotherapy initiation (sub-interval). Results indicated that Black patients had significantly longer wait times to initiate chemotherapy after diagnosis compared to White patients, which was expected based on results from the first study. In addition, Hispanic and Asian/Pacific Islander patients also had significantly longer wait times in this overall interval compared to White patients. This indicated that

even among minorities that were likely to receive chemotherapy within 4 months of diagnosis (as shown in the first study), there were still longer wait times to initiate chemotherapy during those 4 months. Given that delaying chemotherapy by a matter of weeks significantly reduces survival, our findings indicate opportunity for improvement in timeliness of chemotherapy receipt for these patient groups. We then assessed which sub-intervals were likely to contribute to chemotherapy delays. We found that Black and Hispanic patients had longer wait times between diagnosis and surgical resection, and Black and Asian patients had longer wait times between surgical resection and chemotherapy initiation, compared to White patients. A secondary yet important finding was that a larger proportion of Black patients were diagnosed at surgery, which is in line with known disparities in timely colon cancer screening and diagnosis.

In the third study, we demonstrated trends of timely chemotherapy receipt over a recent 10-year period and assessed whether changes in rates occurred after the NQF endorsed a guideline that incorporated a timeframe for initiating chemotherapy. We found that rates of timely chemotherapy receipt did not change (neither immediately nor in trend) from pre- to post- guideline years. Unadjusted trends also indicated that disparities between Black and White patients in timely chemotherapy initiation did not narrow over time.

IMPLICATIONS & FUTURE DIRECTIONS

Measuring Timeliness of Care

Based on the findings of this dissertation, there are measurement considerations to address for this specific guideline (and potentially other time-based guidelines). Although there are a lack of quality measures assessing timeliness of care [2, 59], guidelines such as the one assessed in this research can guide a more standardized definition and

reporting of timeliness and delayed care. The way this guideline is currently measured and reported by health systems, however, masks the extent of delays, particularly racial/ethnic disparities in delays. We recognized the potential of this guideline to quantify delay, and altered its measurement in this research so that delays were distinguished from omitted chemotherapy. With this approach, we were able to specifically define and measure delays and found racial disparities in delayed chemotherapy initiation. However, it became apparent from our second study that even measuring delays categorically as we did in our first study did not fully capture the extent of timeliness disparities. We found that during the first 4 months of diagnosis, Hispanic and Asian patients experienced longer wait times to start chemotherapy compared to White patients. These are disparities in timeliness of care which were masked with our categorical measure of delay in the first study. Given that delaying chemotherapy by a matter of weeks is linked to significantly reduced patient survival, findings from this research suggest the importance of creating quality measures that are able to fully capture the timeliness quality domain.

Another important implication for measuring timeliness of care were the findings from the second paper showing a large proportion of patients had the same diagnosis and surgery date (a zero-day difference between the diagnosis date and surgery date). Without considering what this means, it would artificially appear that these patients had more timely surgery after diagnosis compared to patients who had a longer time interval between diagnosis and surgery (e.g. 14 days). In fact, it is the opposite, where those diagnosed at surgery did not receive timely care, but received it after it was too late (majority of these cases had an emergency or urgent colon resection). Studies that assess timeliness of surgery for colon cancer handle these cases by excluding them from the

study. When chemotherapy initiation is the main focus of the study, however, it does not necessarily make sense to exclude these patients. Also, when assessing wait time differences from diagnosis to surgery, it is important to consider the zeros so that racial disparities in both unplanned surgeries and longer wait times for the planned surgeries are not masked. In addition, the extent of disparities in time to initiate chemotherapy may also get masked. For example, patients diagnosed at surgery appear to receive adjuvant chemotherapy sooner than those diagnosed well in advance, again artificially suggesting better quality of care for patients with a delayed diagnosis. It will be important to create quality measures that encompass both timely access to surgical resection and adjuvant chemotherapy to assess overall quality of cancer care and disparities.

Addressing Disparities through Performance Measures

The wide use of guidelines in the past two decades has been critical to systematically examine and quantify the quality of health care in the U.S., however, larger efforts are needed to reduce quality of care disparities. Disparities are not systematically assessed within health care institutions so that smaller populations that are not achieving recommended guidelines are missed and so are opportunities to intervene. Although the guideline examined in this dissertation was not successful in reducing disparities, future directions outlined by NQF for addressing health care disparities are promising. In a recent comprehensive report, NQF outlined a roadmap for using performance measures to incentivize achieving equity through accountability [80].The roadmap suggests the following actions for stakeholders: identify and prioritize reducing health disparities; implement evidence-based interventions to reduce disparities; invest in the development and use of health equity performance measures; incentivize the reduction of health disparities and achievement of health equity. A few of the ten

recommendations for implementing this roadmap include redesign payment models to support health equity; link health equity measures to accreditation programs; support closing disparities by providing additional payments to providers who care for patients with social risk factors; ensure organizations disproportionately serving individuals with social risk can compete in value-based purchasing programs. The NQF report acknowledges, "performance measurement in healthcare, while critical to monitoring and reducing disparities, is one of many tools needed to eliminate health disparities… the causes of disparities represent complex interactions among institutional, historical, and sociopolitical factors that can only be fully addressed through a variety of mechanisms" [80].

Outcome Measures

This research focused on the process measure piece of Donabedian's model for measuring health care quality of care [92]. Other components of Donabedian's model, such as patient outcomes should be considered as well. Currently we know that not receiving chemotherapy partly explains some of the Black-White disparities in survival. Additional work to understand whether delays to surgery and chemotherapy initiation play a role in survival disparities will be important. Research is also needed to measure and assess mental health outcomes that are associated with receiving delayed care.

Barriers to Care

Findings from this research suggest intervention efforts are needed in different parts of the cancer care continuum for different sub-populations. In order to inform intervention efforts, modifiable barriers to timely surgery and adjuvant chemotherapy receipt in different minority populations must be assessed. These include structural, cognitive, and financial barriers to access that are associated with health care disparities

[60]. Examples of structural barriers include continuity of care, multi-step care processes, multiple locations for tests and specialists, operating hours of health care facility, waiting time, transportation [60]. Examples of cognitive barriers include understanding of treatment, availability of translated materials, cross-cultural communication skills, racial/ethnic concordance of provider [60]. Financial barriers could be higher cost-sharing for more convenient treatments, such as oral chemotherapy.

Interventions to address disparities and such barriers are limited, however one study, the Patient Navigation Research Program (PNRP), a multicenter clinical trial, used navigators to identify and address barriers to timely diagnosis and treatment for patients with breast, cervical, colorectal, and prostate cancers [63]. Navigator services included "arranging financial support, scheduling and arranging for transportation to scheduled appointments, coordinating care among providers, arranging for interpreter services, and linking to community resources" [63]. The study found that navigators had a modest effect among those that already had delayed care (91-365 days) on time to diagnosis and treatment initiation compared to the control arm. However, the navigators did not have an effect on timely diagnosis or treatment initiation in the first 90 days. Barriers to timely care identified in the study included: financial, medical/mental health comorbidities, language/interpreter issues.

More consideration should go into understanding doctor-patient communication barriers and patient satisfaction with care [61]. Donabedian points out that premature termination of care, and other forms of noncompliance might suggest patient dissatisfaction [61]. Some studies have started to assess the negative effects of provider implicit bias [93, 94] and patient mistrust [94, 95] which are important to consider during critical patient-provider interactions about treatments. Interventions to increase active

patient participation and improve patient-provider communication between Black patients and non-Black oncologists can have positive results [62]. In addition, while this dissertation focused on chemotherapy initiation, disparities in chemotherapy *completion* rates and follow-up care are important to assess [11, 44, 64], and should also be considered in equity-focused interventions.

Current Efforts to Follow

The Center for Medicare & Medicaid Innovation (CMS Innovation Center) is piloting a 5-year program with value-based payment models with the aim of improving patient-centered cancer care that is high quality, highly coordinated, at same or lower cost to Medicare [96]. The pilot, called the Oncology Care Model (OCM) began in 2016, and focuses on episodes of care surrounding chemotherapy administration. Participating practices in the pilot program commit to provide care coordination, patient navigators, adherence to national treatment guidelines, as well as 24/7 access to a clinician that has access to patient medical records. How this program shifts practices in the way they treat and coordinate patient care, and whether advances are equitable, will be important to monitor in the coming years.

Next Steps

Based on the findings from this dissertation, some new research questions to examine include:

1. Do disparities in delayed resections and adjuvant chemotherapy initiation explain some of the Black-White survival differences?
2. How can a quality measure capture the full extent of delays, particularly where treatment timeliness is important for patient survival?

3. How can a quality measure with a focus on timeliness of chemotherapy initiation or surgery account for unplanned surgical resections?
4. What are the barriers to timely surgery and chemotherapy receipt for the different racial/ethnic populations?

CONCLUSION

This dissertation found persisting and new disparities by race/ethnicity in receiving timely cancer treatment in the United States. Black patients continue to receive sub-optimal health care across the cancer care continuum from lower cancer screening rates, late stage diagnosis, delayed and unplanned tumor resections, not receiving chemotherapy, and receiving delayed chemotherapy. Asian and Hispanic patients also experienced delays in different parts of the cancer care continuum. Focused efforts to systematically assess and address barriers to receiving standard and timely cancer care for different racial/ethnic populations are still in need.

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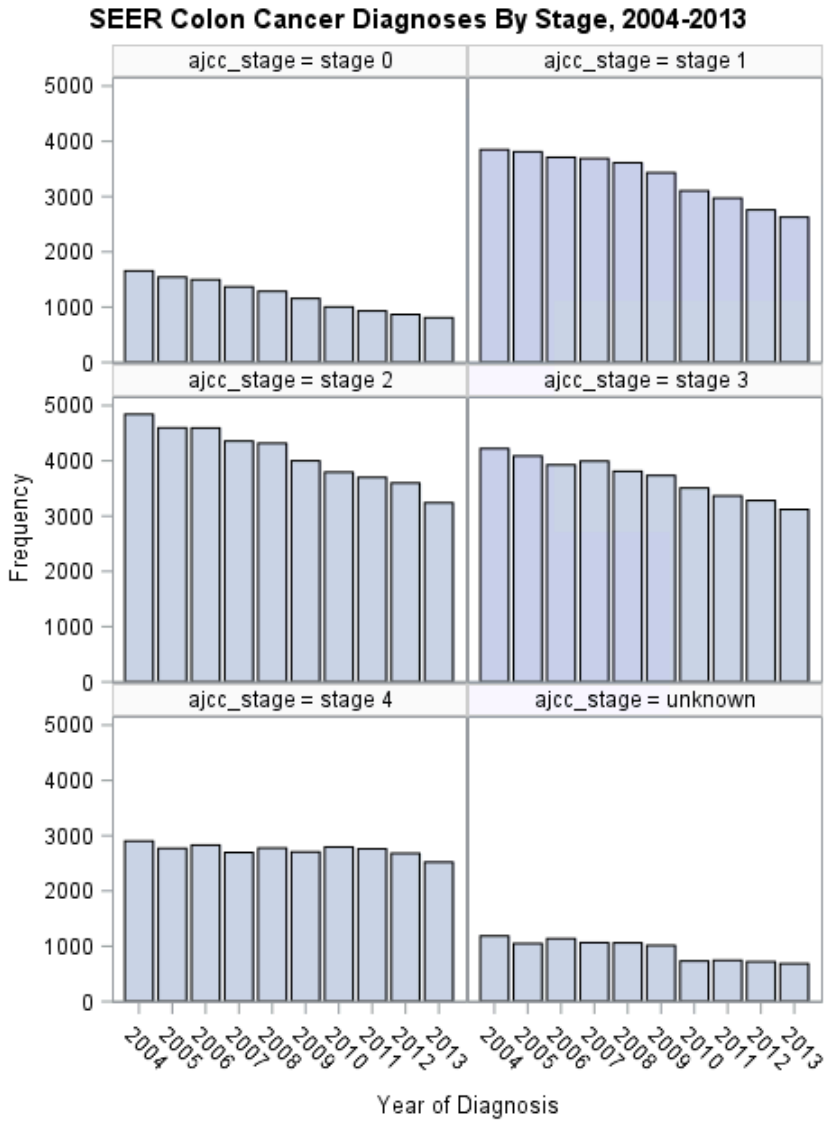
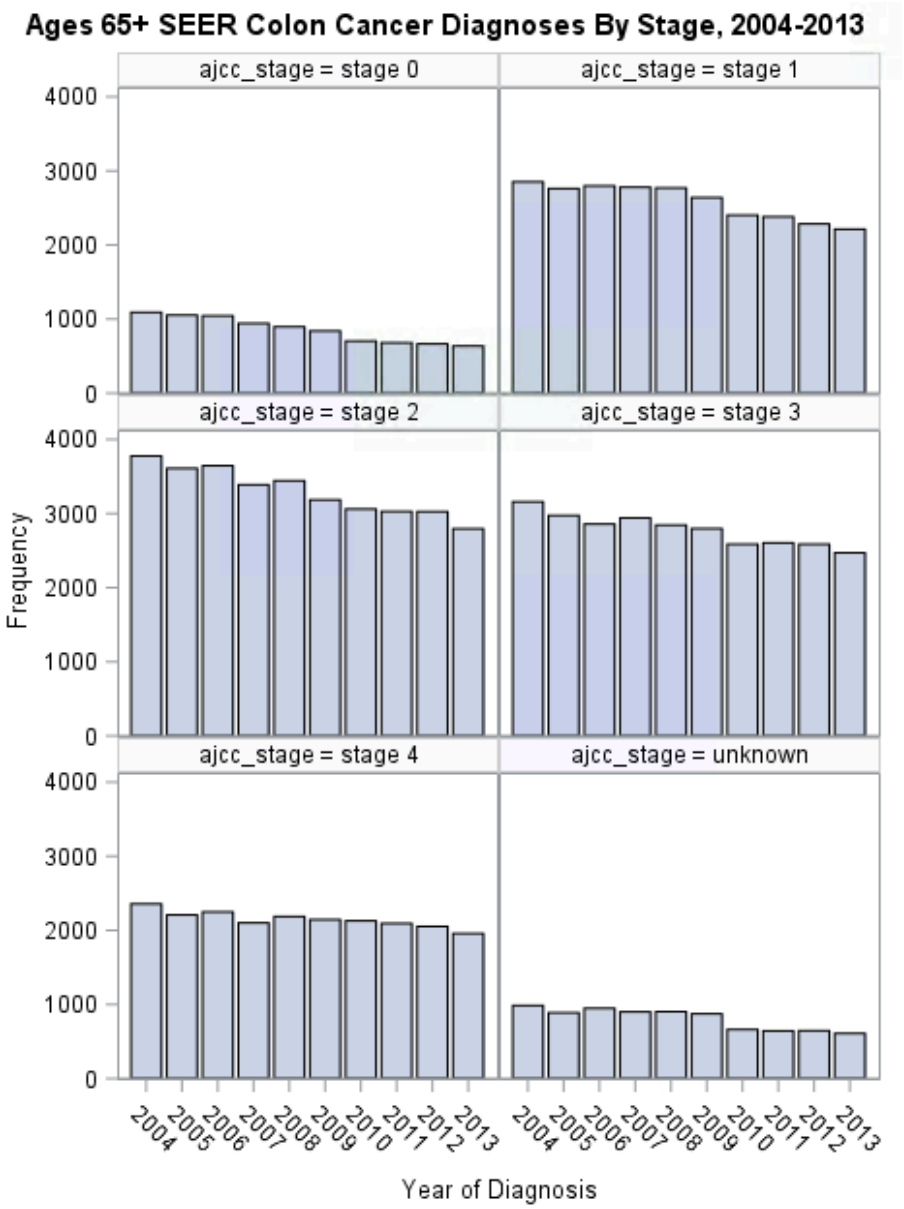
APPENDICES

APPENDIX A. Frequency of colon cancer diagnoses in SEER by stage, 2004-2013

Below are panels showing the frequency of colon cancer diagnoses in SEER by stage for all ages and for ages 65+ for years 2004-2013. The frequency of colon cancer diagnoses for all stages decreased over time between 2004-2013. Smaller decreases are seen for stage IVs compared to the other stages.



Note: all ages; first primary cancer only; not diagnosed at autopsy or death certificate. Both AJCC 6th (2004-2009) and 7th edition (2010-2013) staging variables were used.
Total number of colon cancer diagnoses, all stages (2004-2013): 160,555
Total number of stage III colon cancer diagnoses (2004-2013): 37,051 (23% of all colon cancer cases)



Note: ages 65+; first primary cancer only; not diagnosed at autopsy or death certificate.
Both AJCC 6th (2004-2009) and 7th edition (2010-2013) staging variables were used.
Total number of colon cancer diagnoses, all stages (2004-2013), ages 65+: 124,715 (77% of all colon cancer cases)
Total number of stage III colon cancer diagnoses (2004-2013), ages 65+: 27,819

APPENDIX B. Details of cohort eligibility criteria: selecting stage III diagnoses, date of diagnosis, excluding deaths within 4 months of diagnosis, selecting surgical resection codes and date, excluding those that had surgery or chemotherapy before diagnosis.

Selecting Stage III diagnoses with AJCC 6th and 7th Edition Criteria

AJCC 6th edition variable: dajccstg1; codes: 50-54 were used (note: code 50 is listed in 2014 and 2016 pedsf attachment A files, but does not appear in frequencies of dajccstg1 variable).

AJCC 7th edition variable: dajcc7_01; codes: 500-542 were used.

Both 6th and 7th edition staging criteria were used since staging criteria changed during the study period. In the study cohort, there was a small discrepancy in staging between the two editions, otherwise staging was the same. 182 people were staged as Stage Unknown ("99") or Not Applicable ("88") or as Stage IIb ("33") with AJCC 6th ed staging variable (dajccstg1) but were staged as one of the Stage III codes (500-542) in AJCC 7th ed. variable (dajcc7_01).

Date of Diagnosis

There are no dates of diagnosis in Medicare, only dates of claims. SEER does not have the exact diagnosis date, but has the month and year of diagnosis (60 people were missing a month of diagnosis). There is a 90% agreement within one month of diagnosis between SEER diagnosis date and first Medicare claim date with a cancer diagnosis [97].

In this dissertation, the first Medicare claim date with a colon cancer diagnosis was used as the date of diagnosis after conducting sensitivity analyses between SEER and Medicare dates. See sensitivity analysis under Appendix F (Paper 2).

Death within 4 Months of Diagnosis

Those that died within 4 months of diagnosis were excluded from the studies in this dissertation, in line with CoC guideline specs [22]. In the 2007-2013 study cohort, 9% of those that died within 4 months of diagnosis had received adjuvant chemotherapy. See Appendix F (Paper 2) for sensitivity analysis results.

Surgical Resection

Codes

Claims with the following ICD-9-CM procedure codes were pulled for the surgery inclusion criteria with variables: SRGCDE1-SRGCDE6	
45.71-45.79	open and other partial excision of large intestine
45.81-45.83	total intra-abdominal colectomy
17.31-17.36, 17.39	laparoscopic partial excision of large intestine
The following codes were not included (n=70 for 2004-2013). Other recent studies also do not include these.	
45.41-45.43, 45.49	local excision or destruction of lesion or tissue or large intestine
45.61	multiple segmental resection of small intestine

Admission Date

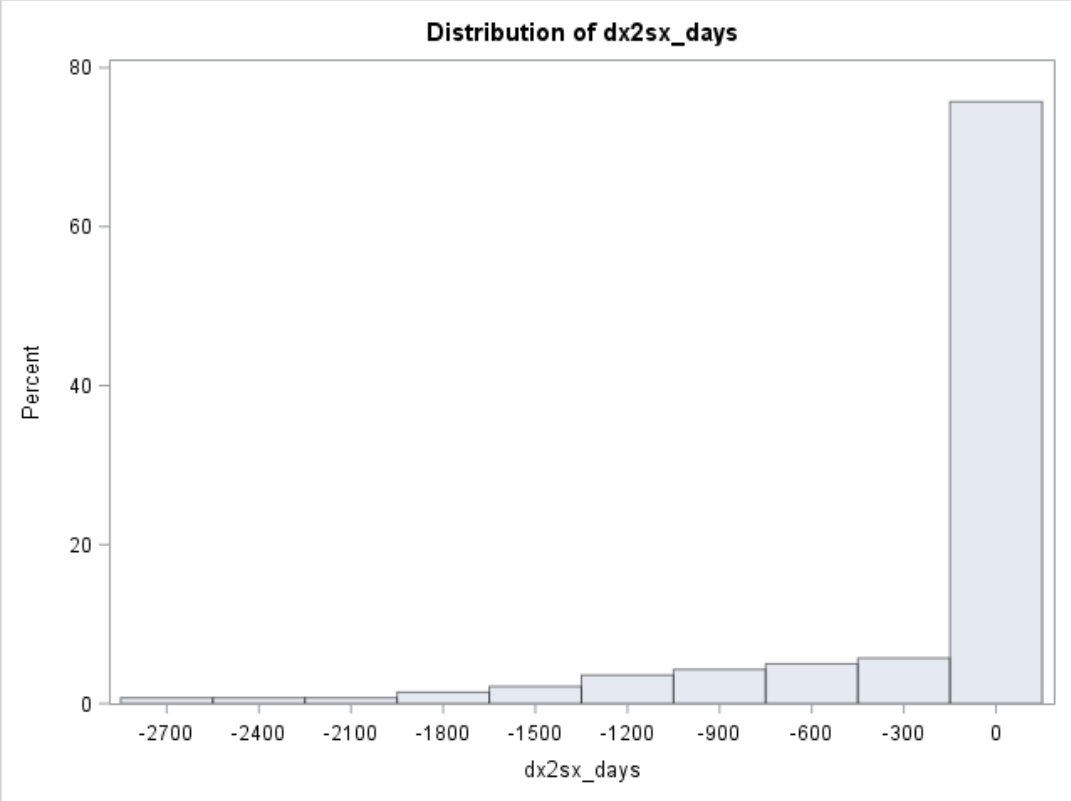
The surgery admission date was used in this dissertation as the surgery date instead of using the surgery date variables. Medicare claims have both an admission date and surgery dates. All patients in the study had an admission date. Patients without a corresponding surgery date (n=58 for 2004-2013) were excluded.

Surgery Admissions before Date of Diagnosis

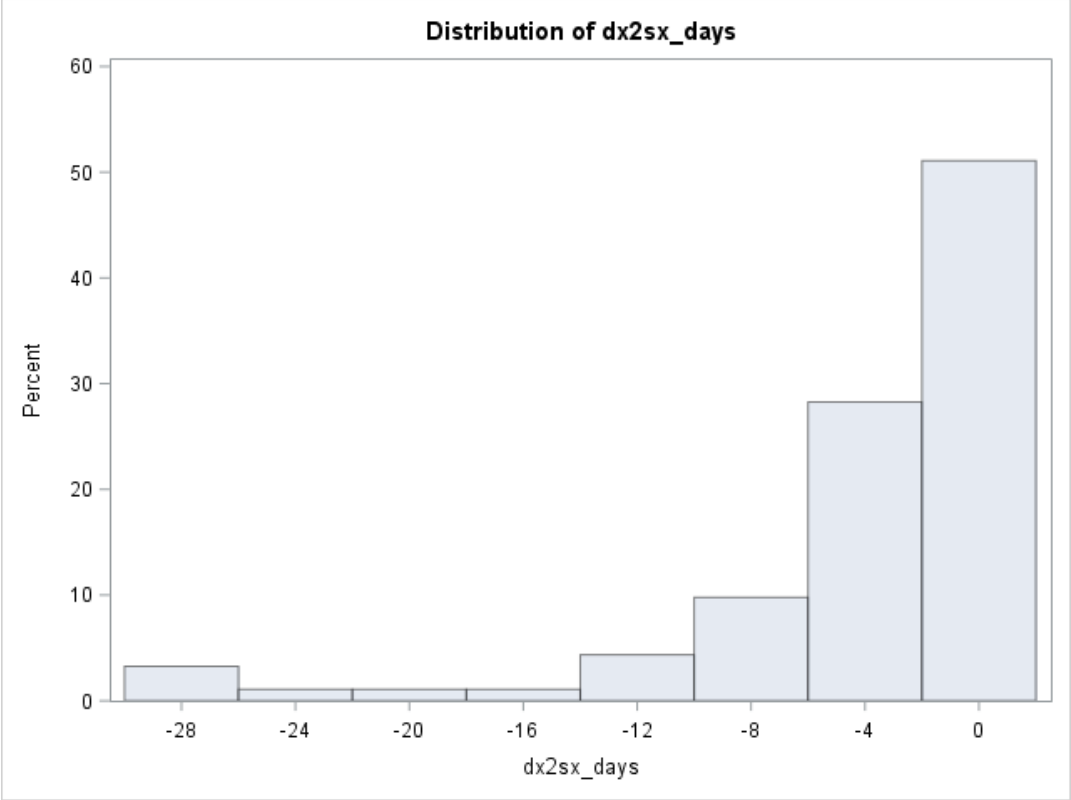
There were n=87 for 2004-2013 and n=73 for 2007-2013 that had a surgery admission before diagnosis, and were excluded. Sensitivity analysis in paper 1 did not show changes in estimates when this group was excluded.

Among all that had admissions before diagnosis, most were diagnosed within a short period of time (usually 1-3 days), so this group could have been included, however paper 2 outcomes required positive counts between time intervals. Re-coding these to 0 could have been an option. Majority of this group (79%) had emergent/urgent surgery. Many had bowel obstruction admitting diagnosis or abdominal pain unspecified site. However, a thorough examination of admitting diagnosis codes was not conducted.

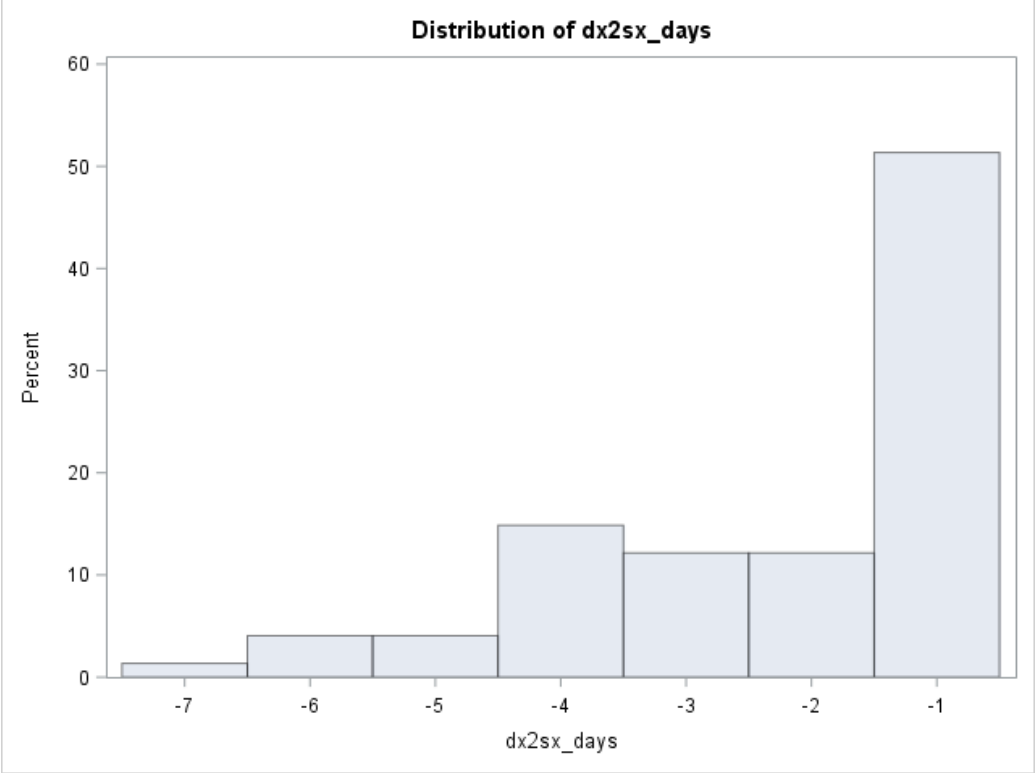
All negative counts for diagnosis to surgery time interval (days), 2004-2013



Negative counts within 30 days before diagnosis date, 2004-2013



Negative counts within 1 week before diagnosis date, 2004-2013

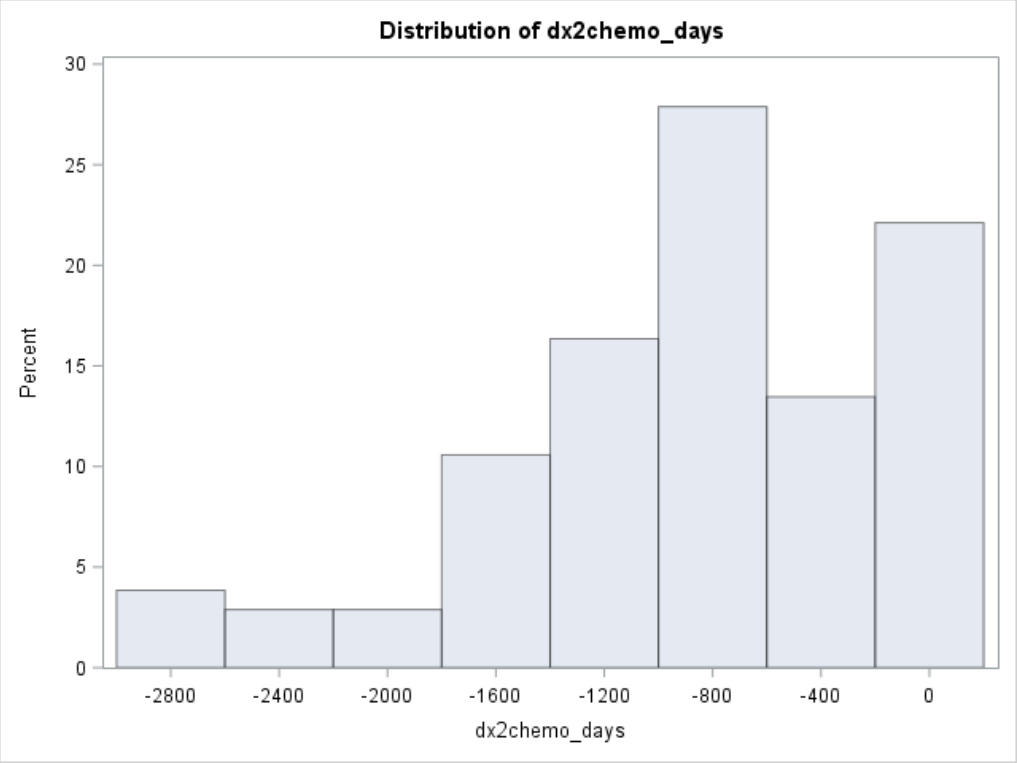


Other details related to surgery - see Appendix F (Paper 2).

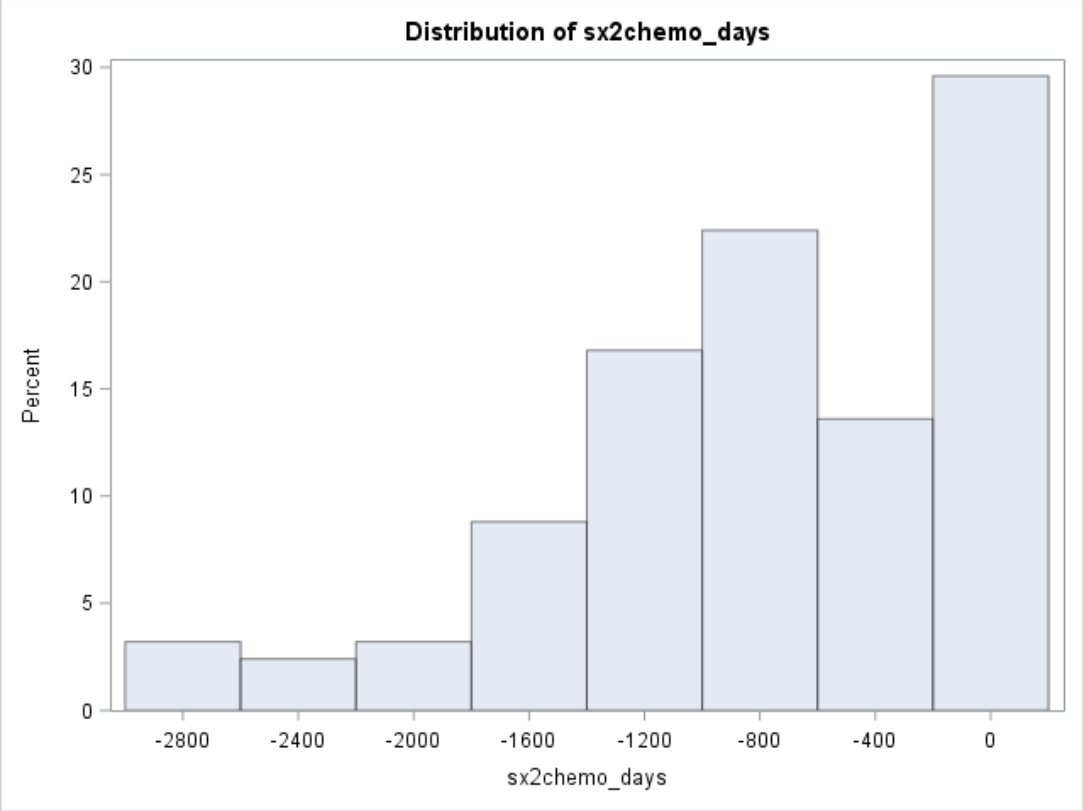
Adjuvant Chemotherapy

Excluded 114 people (2007-2013 cohort) and 132 (2004-2013 cohort) that had chemotherapy before diagnosis or before surgery since the normal pattern for treating stage III colon cancer is surgery first, then chemotherapy. Among the 114 from 2007-2013, 66% had chemotherapy more than 1 year before diagnosis or surgery, while 34% received it within 1 year prior to diagnosis or surgery. Other details related to chemotherapy: see Appendix C

Distribution of chemotherapy receipt before diagnosis, 2007-2013



Distribution of chemotherapy receipt before surgery, 2007-2013



APPENDIX C. Adjuvant chemotherapy details. Number of chemotherapy codes in each of the claims files: MedPAR, Outpatient, National Claims History (NCH), Durable Medical Equipment (DME). Table with list of chemotherapy codes used. Chemotherapy coding change details. Defining chemotherapy receipt beyond 12 months of diagnosis as non-receipt.

Total number of chemotherapy claims in Medicare files, 2004-2014

Medicare claims files	Number of chemotherapy claims
MedPAR	22,636
Outpatient	1,668,145
NCH	4,902,594
DME	124,427
Total	6,717,802

Note: not restricted to any specific patient population.

2004-2013 study cohort: number of first chemotherapy claims, 2004-2014

Medicare claims files	Number of first chemotherapy claims
MedPAR	369
Outpatient	2,911
NCH	6,318
DME	2,543
Total	12,141

Numbers are after selecting patients' first claim with a chemotherapy code in each claims file. To obtain patients' very first chemotherapy claim, the first date among these files was then selected as the date of chemotherapy initiation.

Note: Numbers are before selecting the very first chemotherapy claim and before complete exclusion criteria were implemented (i.e. death within 4 months of diagnosis; resection admission before diagnosis date or 12 months after diagnosis date; chemo before resection or diagnosis date; small race/ethnicity categories).

Medicare Claims Chemotherapy Codes

MedPAR
Surgery code: 9925
Diagnostic codes: v581, v5811, v5812, v662, v672
Outpatient
Procedure code: 9925
Diagnostic codes: v581, v5811, v5812, v662, v672
Center: 0331, 0332
Healthcare Common Procedure Coding System (HCPCS): 36260, 95990, 95991, 96400 – 96549 C1167, C9127, C9205, C9214, C9215, C9257, C9414, C9418, C9425, C9427, C9431, C9432, C9440

E0782 - E0786 G0355 - G0362 J0207, J0640, J0641, J1190, J8520, J8521, J8530, J8565, J8600, J8650, J8700, J8999, J9000 - J9999 Q0083, Q0084, Q0085, Q2024, S0177
NCH
HCPCS: 36260, 95990, 95991, 96400 - 96549 C1167, C9127, C9205, C9214, C9215, C9257, C9414, C9418, C9425, C9427, C9431, C9432, C9440 E0782 - E0786 G0355 - G0362 J0207, J0640, J0641, J1190, J8520, J8521, J8530, J8565, J8600, J8650, J8700, J8999, J9000 - J9999 Q0083, Q0084, Q0085, Q2024, S0177
DME
National Drug Code (NDC): 00179165270, 00179165271, 00179165272, 00078040105, 00078040134, 00085300101, 00085300102, 00085300401, 00085300402, 00085125201, 00085125202, 00085151901, 00085151902, 00085133601, 00085133602, 00085142501, 00085142502, 00085143001, 00085143002, 11326124801, 11326124802, 11326124401, 11326124402, 11326125901, 11326125902, 11326125201, 11326125202, 15050301, 15309145, 17101050301, 17101050302, 17101050401, 17088005001, 17088003101, 17088004901, 378326694, 4110013, 4110016, 4110020, 4110022, 4110051, 4110113, 4110116, 4110150, 4110151, 53808041101, 54868414301, 54868414303, 55567005002, 55361163904, 57423000104, 51079096501, 51079096505, 54868535400, 54868534801, 53922151901, 53922151902, 53922136601, 53922136602, 53922300401, 53922300402, 53922141701, 53922143001, 53922143002, 53922142501, 53922142502, 51129309901, 51129309902, 54868526001 – 54868526009, 54868414202 – 54868414206, 54868542700 – 54868542703, 54868528900 - 54868528904 6049117001, 6049117028, 66828003001, 78043815, 85125901, 85141701

Note: Codes from Parsons, 2011 dissertation [98]. Checked codes from other recent studies [57, 99].

Coding Changes, 2004-2006

Coding changes for chemotherapy that occurred between 2004 and 2005 were checked during Paper 3 analysis. Changes in Q codes, CPT codes, and G codes did occur between 2004-2006, and most of these were accounted for in our original chemotherapy codes.

Historical changes in coding are scattered across resources and documents. Researchers could benefit from having this information in an organized and easily searchable format.

G-codes (G9021-G9032) that were not in the original code were checked. These are not chemo codes, but codes for assessment of chemo symptoms/side effects. Missing these could result in an underestimate for 2005 chemotherapy rates [100]. Conclusion: these G-codes only added 1 chemo claim from NCH claims, and was not added to the final analyses.

Oral chemotherapy was also checked. Oral chemotherapy is covered by Medicare Part B if there is also an intravenous (IV) version available. Oral Capacetabine has a J-code and NDC codes that were included in analyses. Part D claims have yet to be validated to identify oral chemotherapy without IV version. Part D claims were checked with available NDC codes, and 17 claims were found for 2004-2014. Those were not included in the study.

Defining Chemotherapy Receipt

Chemotherapy receipt beyond 12 months of diagnosis was defined as non-receipt. Most patients had their surgeries within 2-3 months of diagnosis, so chemotherapy receipt beyond 12 months of diagnosis could be for recurrence. Sensitivity analysis with different cut-off months for time from diagnosis to chemotherapy were done with Paper 1 outcome. The following cut-offs were checked: 6, 12, 18, and 24 months. Main racial/ethnic differences in the outcome did not change with or without one of the cut-offs. In line with other studies, a cut-off of 12 months from diagnosis was chosen.

APPENDIX D. Race/ethnicity details. Managing small cell sizes and categorizing independent variables (marital status, census tract poverty level, residence, SEER registry, tumor location, hospital length of stay (LOS), Charlson comorbidity score). Table of original independent variable categories by race/ethnicity.

Race/Ethnicity

There are many race/ethnicity variables in SEER pedsf documentation and pedsf attachment A with limited details. The SEER race recode variable (rac_recb) was used in this dissertation since it distinguishes between Hispanic and non-Hispanic White (while other race variables in SEER such as srace do not distinguish Hispanic ethnicity). Race categories for rac_recb variable line up with srace variable race categories.

Hispanic Origin

With 2004-2013 cohort, a cross-tab between the SEER race recode variable (rac_recb) and Hispanic origin variable (origin) was done. All people in category 11 (Caucasian, Spanish origin or surname) of rac_recb fall into one of the Hispanic origin variable categories. Majority are in category 5 of origin (Mexican) or category 6 of origin (Spanish, NOS; Hispanic, NOS; Latino, NOS - there is evidence, other than surname or maiden name, that the person is Hispanic but he/she cannot be assigned to any of the categories 1-5).

Smaller percentages fall into the other categories: Puerto Rican, Cuban, South or Central American (except Brazil); Other specified Spanish/Hispanic origin (includes European, excludes Dominican Republic); Spanish surname only - effective with diagnosis on or after 1/1/1994, the only evidence of the person's Hispanic origin is the surname or maiden name and there is no contrary evidence that the patient is not Hispanic. 5% of Hispanic cohort fall into the Spanish surname only category. None fall into category 8 (Dominican Republic) or category 9 (Unknown).

In SEER, there is another race/ethnicity variable (race), that is labeled Medicare Race in the dataset, which includes a Hispanic category. A cross-tab was done between this variable and Hispanic origin variable (origin). A large number of people of Hispanic origin were placed in the White category of race variable instead of the Hispanic category, which is why the number of Hispanics with this variable (race) is low. People who were not of Hispanic origin were in the Hispanic category of the race variable. For these reasons, I do not recommend using the race variable (variable name: race; labeled Medicare Race).

For 2007-2013 cohort, there were <11 Black Hispanics and < 11 Asian Hispanics, which were coded by their respective races instead of ethnicity.

Asian/Pacific Islander
The Asian/Pacific Islander populations were grouped together due to small cell sizes for the covariates. Note: SEER also has a variable (srace) to identify the specific ethnicities under the Other Asian or Pacific Islander category of rac_recb variable.

American Indian/Alaska Native
2007-2013 cohort: American Indian/Alaska Native (N=24) and "other" (N<11) race/ethnicity categories were excluded from both study cohorts due to small cell sizes.

Census Tract Poverty Level
Because of small cell sizes in 0-5% poverty for Blacks and Hispanics, 0-<5% and 5-<10% categories were combined. The "unknown" category (which also has small cell sizes for Blacks and Hispanics) were combined with 20-100% poverty.

Urban/Rural
For the urban/rural variable in SEER (urbrur), there were small Hispanic and Asian cell sizes in Less Urban and Rural categories. As other studies have done, a non-metropolitan and metropolitan variable was created by combining the following categories: Urban, Less Urban, Rural, and 2 missing (Non-Metropolitan); and Big Metro and Metro (Metropolitan). pedsf summary file has further details of how this variable (urbrur), was re-coded from the 2003 Rural/Urban Continuum Codes.

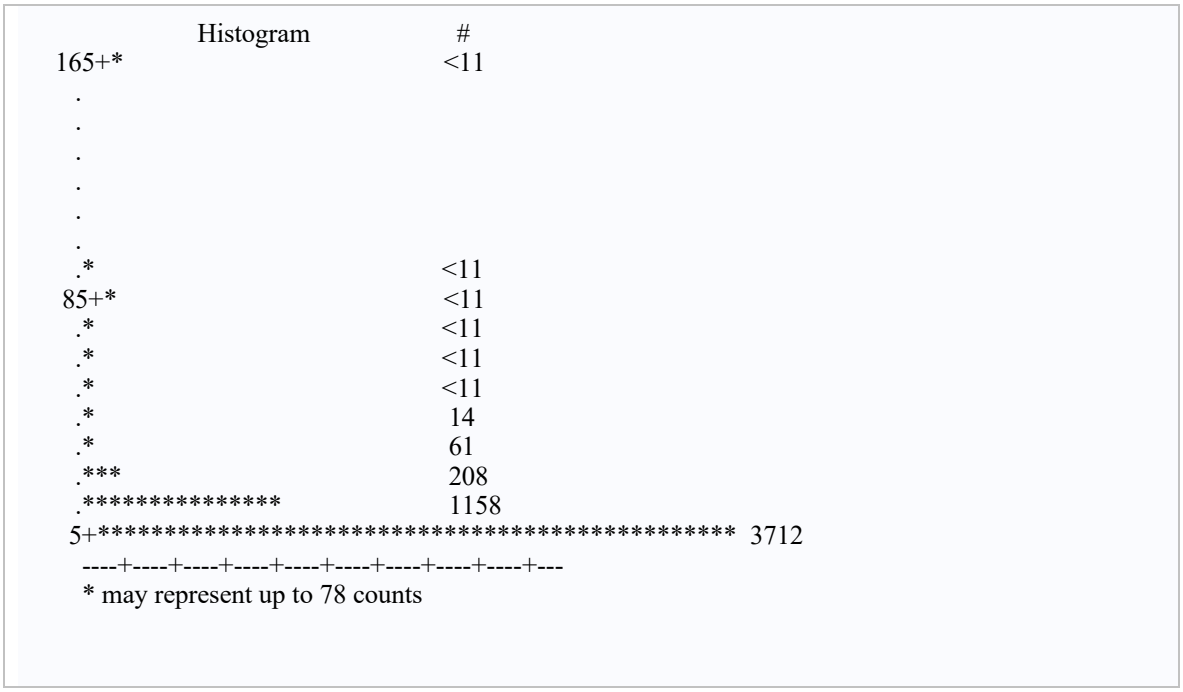
SEER Registry
Due to very small cell sizes in specific registries for certain racial/ethnic groups, analyses in this dissertation did not include registry. A sensitivity analysis was conducted with paper 1 outcome stratified by registry. The Black-White disparity was seen in all registries. Estimates barely changed from unadjusted to adjusting for SEER registry variable.

Tumor Location
Tumor location variable was re-coded as other studies have done [101, 102]. Due to small cell size for Unknown (NOS and crosses both), it was combined with the most common side, which is the right side of colon.

Marital Status
Due to small cell sizes in Single and Unknown categories for minorities, these categories were combined with Formerly Married.

Length of Stay (LOS)
In line with other studies, continuous LOS was used in Paper 1 and 2 analyses. Sensitivity analyses with Paper 1 outcome showed change, but not drastic changes between using a continuous verses categorical variable. The categorical variable is shown in the descriptive tables of all papers for descriptive purposes.

Sensitivity analysis was conducted by removing outliers for LOS that were above 60 days. Removal of outliers did not change results for paper 1 or 2 outcomes, so outliers were kept in final analysis.



Charlson Comorbidity Index (CCI)

129 people had a missing CCI score (2004-2013). These were coded as 0, as other studies have done [37]. CCI frequencies line up with other recent studies.

Typical options in literature to categorize CCI : 0, 1, 2+ or 0, 1, 2, 3+. The latter was chosen so the racial disparity in the 3+ category was not masked. There is a substantial racial/ethnic variation in the 0 category and in the 3+ category (and not much variation in the 1 or 2 categories).

Charlson comorbidity score

Charlson	Frequency	Percent	Cumulative Frequency	Cumulative Percent
0	3671	46.40	3671	46.40
1	2166	27.38	5837	73.77
2	1027	12.98	6864	86.75
3	496	6.27	7360	93.02
4	262	3.31	7622	96.33
5	146	1.85	7768	98.18
6	69	0.87	7837	99.05
7	38	0.48	7875	99.53
8	15	0.19	7890	99.72

Charlson comorbidity score

Charlson	Frequency	Percent	Cumulative Frequency	Cumulative Percent
9	13	0.16	7903	99.89
10	<11	-	-	-
11	<11	-	-	-
12	<11	-	-	100.00

Frequency Missing = 129

Below is how SEER-Medicare weighted the Charlson Comorbidity Index [55] (code from the end of the macro):

```
*** Calculate the coefficient for prior conditions;
   Charlson = (acute_mi or history_mi) +
            (chf) +
            (pvd) +
            (cvd) +
            (copd) +
            (dementia) +
            (diabetes and not diabetes_comp) +
            (mild_liver_disease and not liver_disease) +
            (ulcers) +
            (rheum_disease) +
            (paralysis*2) +
            (renal_disease*2) +
            (diabetes_comp*2) +
            (liver_disease*3) +
            (aids*6);
   output;
 end;
```

Original Independent Variables by Race/Ethnicity, Ages 66-79, SEER-Medicare 2007-2013

	Race/Ethnicity			
	White	**Black**	**Hispanic**	**Asian/Pacific Islander**
	N	**N**	**N**	**N**
Marital Status				
Single (never married)	332	96	36	31
Married (including common law)	2,333	173	167	213
Separated	20	11	11	<11
Divorced	343	55	24	21
Widowed	782	138	50	52
Unmarried or domestic partner (same sex or opposite sex or unregistered)	<11	<11	<11	<11
Unknown	149	23	<11	<11
Census Tract Poverty				
0%-<5% poverty	921	26	30	70

	Race/Ethnicity			
	White	Black	Hispanic	Asian/Pacific Islander
	N	N	N	N
5% to <10% poverty	1,065	52	48	86
10% to <20% poverty	1,092	117	92	64
20% to 100% poverty	578	284	90	43
Unknown	304	17	35	62
Rural/Urban				
Big Metro (Urban = 00 or 01)	1,897	275	160	236
Metro (Urban = 02 or 03)	1,192	134	109	78
Urban (Urban = 04 or 05)	244	31	11	<11
Less Urban (Urban = 06 or 07)	491	52	13	<11
Rural (Urban = 08 or 09)	136	<11	<11	<11
Registry				
San Francisco (1973+)	93	11	12	43
Connecticut (1973+)	229	20	<11	<11
Detroit (1973+)	233	69	<11	<11
Hawaii (1973+)	11	<11	<11	50
Iowa (1973+)	363	<11	<11	<11
New Mexico (1973+)	70	<11	52	<11
Seattle (1974+)	228	<11	<11	16
Utah (1973+)	93	<11	<11	<11
Atlanta (1975+)	93	42	<11	<11
San Jose (1988+)	72	<11	18	25
Los Angeles (1988+)	185	18	55	71
Rural Georgia (1992+)	<11	<11	<11	<11
Greater California (2000+)	609	28	86	74
Kentucky (2000+)	437	21	<11	<11
Louisiana (2000+)	300	126	<11	<11
New Jersey (2000+)	580	81	44	14
Greater Georgia (2000+)	357	59	<11	<11
Charlson Comorbidity Index				
0	1,852	163	120	149
1	1,076	144	86	85
2	499	73	34	48
3	256	46	18	15
4	133	32	15	13
5	70	19	11	<11
6	34	<11	<11	<11
7	20	<11	<11	<11
8	11	<11	<11	<11
9	<11	<11	<11	<11
10	<11	<11	<11	<11
11	<11	<11	<11	<11
12	<11	<11	<11	<11
Tumor Location				
180	1,153	124	85	58
182	921	114	69	62
183	217	20	16	<11
184	398	57	24	33
185	160	25	<11	11
186	218	43	16	35
187	815	105	72	110
188	58	<11	<11	<11

	Race/Ethnicity			
	White	Black	Hispanic	Asian/Pacific Islander
	N	N	N	N
189	20	<11	<11	<11
Tumor Grade				
1 = Grade I; grade i; grade 1; well differentiated; differentiated, NOS	190	32	19	<11
2 = Grade II; grade ii; grade 2; moderately differentiated; moderately differentiated; intermediate differentiation	2,497	334	191	230
3 = Grade III; grade iii; grade 3; poorly differentiated; differentiated	1,031	105	69	78
4 = Grade IV; grade iv; grade 4; undifferentiated; anaplastic	163	15	<11	<11
9 = cell type not determined, not stated or not applicable	79	<11	<11	<11

APPENDIX E. Paper 1 Analytic Methods

Ordinal logistic regression vs. multinomial logistic regression

Two analytic options were considered for the categorical outcome in Paper 1: ordinal logistic regression (when the outcome is ordered) and multinomial logistic regression (when the outcome is not ordered). A main assumption for ordinal logistic regression is the proportional odds assumption, meaning ordered logit coefficients are equal across the levels of the outcome. This assumption was tested, and did not hold (Score Test for the Proportional Odds Assumption: p=0.0339). An alternative analytic option for a categorical outcome is multinomial logistic regression, which does not assume proportional odds, and was chosen for Paper 1 analysis.

Checking categorical outcome cell sizes for each predictor.

	Total		
	No Chemo	**Delayed Chemo**	**Guideline-Concordant Chemo**
	N	**N**	**N**
race/ethnicity	810	266	2,942
White			
Black	160	59	293
Hispanic	58	30	216
Asian/Pacific Islander	70	29	233
Gender	507	196	1,790
Male			
Female	591	188	1,894
Age	188	104	1,052
Ages 66-69			
Ages 70-74	345	152	1,418
Ages 75-79	565	128	1,214
Marital Status	486	186	2,252
Married/Domestic Partner			
Not Married	612	198	1,432
Charlson Comorbidity Index	392	136	1,846
0			
1	272	98	1,021
2	168	62	424
3	266	88	393
Year of Diagnosis	186	75	634
2007			

2008	198	60	611
2009	164	53	529
2010	146	52	534
2011	146	41	460
2012	129	51	490
2013	129	52	426
Tumor Location	737	269	2,503
Right			
Left	361	115	1,181
Tumor Grade	765	268	2,531
Well/Moderately Differentiated			
Poorly/Undifferentiated	333	116	1,153
Length of Stay	372	184	1,966
1			
2	474	132	1,439
3	252	68	279
Census Tract Poverty	460	164	1,710
0% to <10% poverty			
10% to <20% poverty	287	104	994
20% to 100% poverty	351	116	980
Rural/Urban Continuum Codes	215	45	748
Non-Metropolitan			
Metropolitan	883	339	2,936

Note: Each cell size for all categorical independent variables is above 10. Smallest cell size is 29 delay for Asian and 30 delay for Hispanic.

Non-perfect separation assumption (no complete or quasi-complete separation):
This assumption is to ensure that predictor categories don't separate perfectly into an outcome category or with little overlap between the outcome categories. Predictor values fall into all the categories of the outcome variable in this study cohort.

Independence of Irrelevant Alternatives (IIA) assumption (adding or removing outcome categories does not affect the odds of other outcome categories):
Long and others have found the Hausman-McFadden test not useful in assessing violation of IIA [103]. Long pointed to McFadden's suggestion of using multinomial regression when the outcomes "can plausibly be assumed to be distinct and weighed independently in the eyes of each decision maker" [104].
Separate binary logistic regression models were run without one of the guideline discordant categories. Results remained close to the multinomial logistic regression results.

Binary Logistic Regression

	Adjuvant Chemotherapy Received After 4 Months vs. Received within 4 Months of Diagnosis	**No Adjuvant Chemotherapy Received vs. Received within 4 Months of Diagnosis**
	OR (95% CI)	OR (95% CI)
White	Ref	Ref
Black	1.74 (1.24 to 2.44)	1.40 (1.10 to 1.78)
Hispanic	1.37 (0.90 to 2.09)	0.83 (0.60 to 1.16)
Asian/ Pacific Islander	1.41 (0.93 to 2.14)	1.15 (0.85 to 1.55)

Note: OR = Odds Ratio. CI = Confidence Interval. * = Statistically Significant. Ref = Reference

Improvement of Fit

Akaike Information Criterion (AIC) and Likelihood Ratio chi-square (LR chi-square) were checked between null model, model with sociodemographic characteristics, and full model with added clinical variables. AIC and LR chi-square indicated better model fit with each addition.

	Akaike Information Criterion (AIC)	Likelihood Ratio chi-square (LR chi-square)
Null model (intercept only)	7892.056	57.8623; p<.0001
+ sociodemographic characteristics	7629.545	302.5114; p<.0001
+ clinical covariates (full model)	7348.149	631.9068; p<.0001

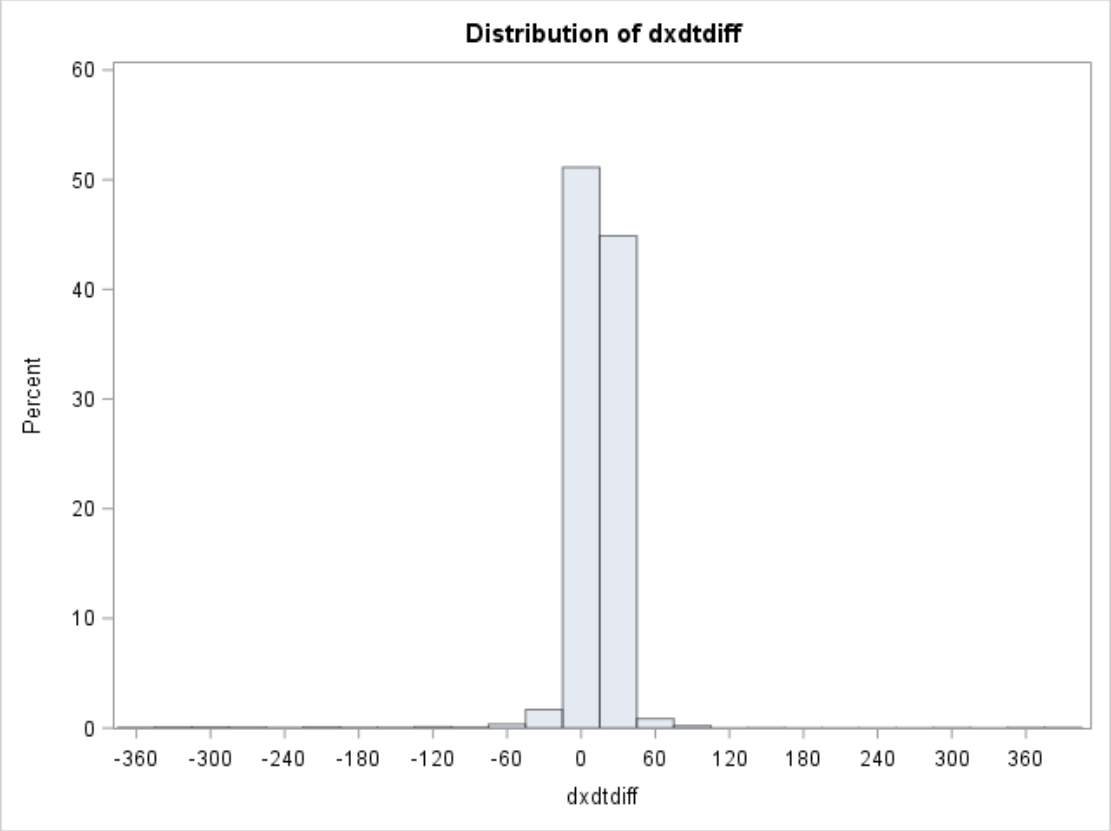
Paper 1 and Paper 2 Selection Criteria

SEER-Medicare Study Selection Flow Chart, 2007-2013	
1. Stage III colon cancer diagnosis between 2007 and 2013	N=26,438
2. Ages 66 - 79 years (guideline applies to those below 80 years of age)	N=11,556
3. Not diagnosed at autopsy and not diagnosed at death certificate	N= 11,500
4. First and only cancer or first of more than one cancer diagnosis	N= 10,823
5. Had surgical resection	N= 10,805
6. Likely to have complete claims	N= 6,282
7. Had a surgical resection claim in Medpar	N= 5,835
8. Alive within 4 months of diagnosis	N=5,424
9. Resection admission not before diagnosis date	N=5,351
10. Resection admission not 12 months after diagnosis date	N=5,309
11. Chemotherapy not received before diagnosis date or before resection admission	N=5,195
12. No small race/ethnicity categories	**N= 5,166**

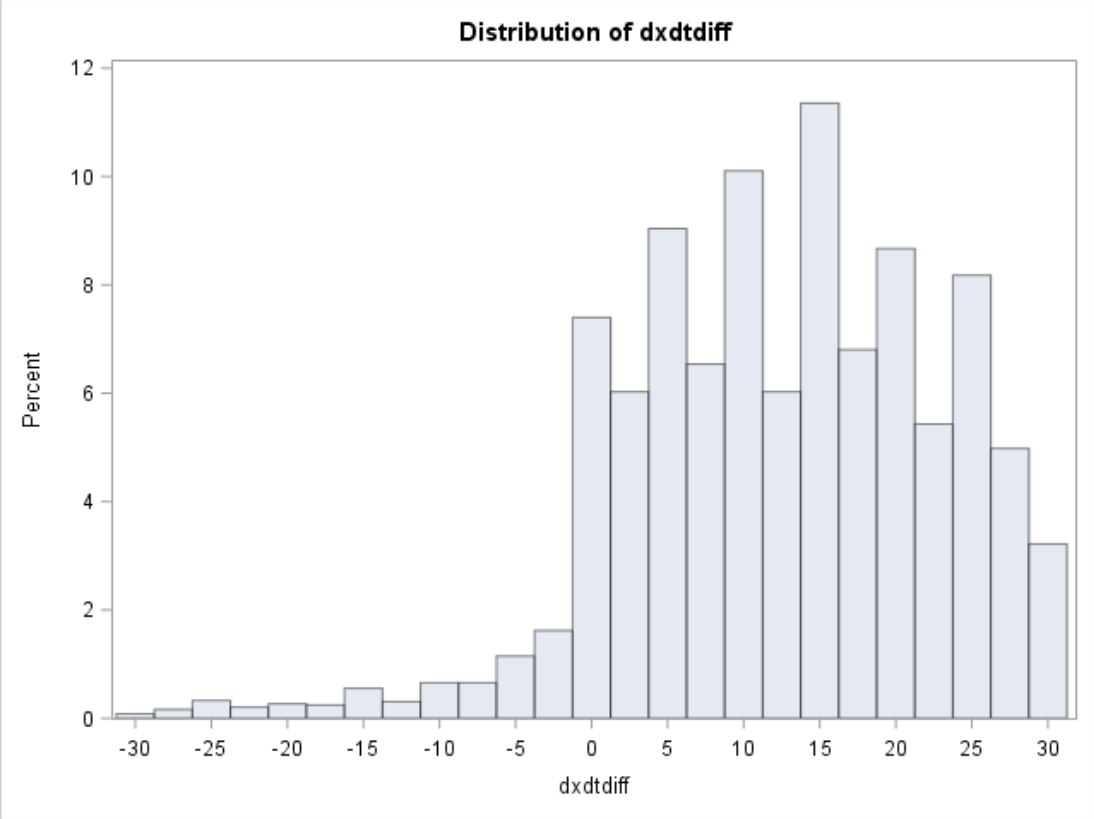
APPENDIX F. Paper 2 Analytic Methods

Diagnosis date comparison: comparing SEER diagnosis date (day 1) and first claim date in Medicare with a colon cancer diagnosis (2007-2013 study cohort)

Difference in days between claims date and SEER date of diagnosis



Difference in days between claims date and SEER date of diagnosis (within 30 days)



Difference: Medicare Date – SEER date with day 01 = 13 days (median)

Mean and median difference in days between Medicare and SEER date by race/ethnicity
Overall: Mean = 12 days; min = -356; max = 392; Median: 13 days
White: Mean = 12 days; min = -356; max = 392; Median: 13 days
Black: Mean = 10 days; min = -336; max = 96; Median: 13 days
Hispanic: Mean = 10 days; min = -327; max = 101; Median: 14 days
Asian: Mean = 14 days; min = -352; max = 383; Median: 15 days

Outcomes Comparison between SEER and Medicare Dates of Diagnosis

Median days [IQR], Kruskal-Wallis Test

DX TO CHEMO	SEER DX DATE	Medicare DX DATE
Overall	77 [62, 99]	63 [48, 84]
White	75 [61, 97]	62 [47, 82]
Black	89 [68, 110]	76 [55, 100]
Hispanic	84 [64, 109]	69 [51, 92]
Asian/PI	80 [65, 102]	67 [50, 87]
	p <.0001	p <.0001

DX TO SX	SEER DX DATE	Medicare DX DATE
Overall	25 [14, 40]	11 [0, 24]
White	25 [14, 39]	10 [0, 23]
Black	23 [13, 42]	8 [0, 28]
Hispanic	28 [17, 45]	14 [0, 30]
Asian/PI	27 [16, 43]	13 [0, 26]
	p=0.0088	p =0.0142

SX TO CHEMO	SEER DX DATE	Medicare DX DATE
Overall	48 [38, 63]	48 [38, 64]
White	47 [37, 62]	47 [37, 63]
Black	54 [41, 74]	54 [41, 76]
Hispanic	51 [40, 69]	50 [39, 68]
Asian/PI	50 [40, 67]	50 [40, 67]
	p<.0001	p<.0001

(not affected by change in dx date)

Conclusion:
Since the outcomes assessed are short time intervals, and there was a median 2-week difference between the SEER date (with day 1) and Medicare date, the Medicare date was chosen as the date of diagnosis. The racial/ethnic differences are similar with either date.

Sensitivity analysis: excluding those that died within 4 months of dx from study cohort versus including them and censoring at death

Cox proportional hazard models: Diagnosis to Chemotherapy Time Interval

	Excluding those that died within 4 months of dx from study cohort	Including those that died within 4 months of dx and censoring
	Adjusted HR (95% CI)	Adjusted HR (95% CI)
White	1.00 (Reference)	1.00 (Reference)
Black	0.713 (0.627-0.811)*	0.716 (0.630-0.813)*
Hispanic	0.788 (0.663-0.936)*	0.794 (0.669-0.943)*
Asian/Pacific Islander	0.649 (0.522-0.807)*	0.658 (0.529-0.817)*

HR=Hazard Ratio. CI=Confidence Interval.
* = Statistically Significant.
All models are fully adjusted for sociodemographic and clinical covariates and includes proportional hazard interaction term.

Cox proportional hazard models: Diagnosis to Surgery Time Interval

	Excluding those that died within 4 months of dx from study cohort	Including those that died within 4 months of dx and censoring
	Adjusted HR (95% CI)	Adjusted HR (95% CI)
White	1.00 (Reference)	1.00 (Reference)
Black	0.882 (0.801-0.973)*	0.872 (0.795-0.957)*
Hispanic	0.843 (0.749-0.950)*	0.840 (0.749-0.944)*
Asian/Pacific Islander	0.939 (0.838-1.053)	0.925 (0.826-1.036)

HR=Hazard Ratio. CI=Confidence Interval.
* = Statistically Significant.
All models are fully adjusted for sociodemographic and clinical covariates.

Cox proportional hazard models: Surgery to Chemotherapy Time Interval

	Excluding those that died within 4 months of dx from study cohort	Including those that died within 4 months of dx and censoring
	Adjusted HR (95% CI)	Adjusted HR (95% CI)
White	1.00 (Reference)	1.00 (Reference)
Black	0.783 (0.689-0.889)*	0.785 (0.692-0.890)*
Hispanic	0.896 (0.759-1.058)	0.903 (0.765-1.066)
Asian/Pacific Islander	0.730 (0.595-0.895)*	0.742 (0.605-0.911)*

HR=Hazard Ratio. CI=Confidence Interval.
* = Statistically Significant.
All models are fully adjusted for sociodemographic and clinical covariates and includes a proportional hazard interaction term.

Emergent/urgent/elective admissions among 2007-2013 cohort by race/ethnicity (after excluding negative counts from diagnosis to surgery).

Admission Type (Medpar variable: ADMTYPE)	White	Black	Hispanic	Asian/Pacific Islander	Total
Emergency	826 (21)	153 (30)	66 (22)	59 (18)	1104 (21)
Urgent	554 (14)	74 (14)	49 (16)	61 (18)	738 (14)
Elective	2630 (65)	285 (56)	189 (62)	211 (64)	3315 (64)
Unknown	<11	<11	<11	<11	<11
Total	4018 (78)	512 (10)	304 (6)	332 (6)	5166 (100)

Note: Frequencies and column percents. Total row shows row percents.

Combining emergency and urgent admissions: White: 35%; Black: 44%; Hispanic: 38%; Asian: 36%; Total: 35%;

Roughly lines up with the race/ethnicity breakdown of zeros days between diagnosis to surgery.

Number of days between diagnosis and surgical resection	White	Black	Hispanic	Asian/Pacific Islander	Total
Zero days between diagnosis and surgery	1375 (34)	212 (41)	97 (32)	105 (32)	1789 (35)
More than zero days between diagnosis and surgery	2643 (66)	300 (59)	207 (68)	227 (68)	3377 (65)
Total	4018 (78)	512 (10)	304 (6)	332 (6)	5166 (100)

Note: Frequencies and column percents. Total row shows row percents. P=0.0046

Emergent/urgent/elective admissions among 2007-2013 cohort by race/ethnicity among those diagnosed on same day as surgery (zero days between diagnosis and surgery)

Admission Type (Medpar variable: ADMTYPE)	White	Black	Hispanic	Asian/Pacific Islander	Total
Emergency	712 (52)	130 (61)	52 (54)	45 (43)	939 (52)
Urgent	305 (22)	38 (18)	25 (26)	41 (39)	409 (23)
Elective	356 (26)	44 (21)	20 (21)	19 (18)	439 (25)
Unknown	<11	<11	<11	<11	<11
Total	1375 (77)	212 (12)	97 (5)	105 (6)	1789 (100)

Note: Frequencies and column percents. Total row shows row percents.
Combining emergency and urgent admissions: White: 74%; Black: 79%; Hispanic: 80%; Asian: 82%; Total: 75%

From Medpar Appendix:
(CLM_IP_ADMSN_TYPE_TB) Claim Inpatient Admission Type Table
0 = Blank
1 = Emergency - The patient required immediate medical intervention as a result of severe, life threatening, or potentially disabling conditions. Generally, the patient was admitted through the emergency room.
2 = Urgent - The patient required immediate attention for the care and treatment of a physical or mental disorder. Generally, the patient was admitted to the first available and suitable accommodation.
3 = Elective - The patient's condition permitted adequate time to schedule the availability of suitable accommodations.
4 = Newborn - Necessitates the use of special source of admission codes.
5 = Trauma Center - visits to a trauma center/hospital as licensed or designated by the State or local government authority authorized to do so, or as verified by the American College of Surgeons and involving a trauma activation.
6 THRU 8 = Reserved
9 = Unknown - Information not available.

Sensitivity analysis: including and excluding zeros, time from diagnosis to surgery outcome

Cox proportional hazard models: diagnosis to surgery time interval

	Including zero days from diagnosis to surgery	Excluding zero days from diagnosis to surgery
	Adjusted HR (95% CI)	Adjusted HR (95% CI)
White	1.00 (Reference)	1.00 (Reference)
Black	0.882 (0.801-0.973)*	0.771 (0.680-0.875)*
Hispanic	0.843 (0.749-0.950)*	0.822 (0.712-0.950)*
Asian/Pacific Islander	0.939 (0.838-1.053)	0.950 (0.827-1.092)

HR=Hazard Ratio. CI=Confidence Interval.
* = Statistically Significant.
All models are fully adjusted for sociodemographic and clinical covariates

Wait times are longer for Black and Hispanic patients after excluding those diagnosed at surgery. Something to consider with evaluation of quality. Excluding zeros from study cohort masks disparities in unplanned surgeries, while including zeros masks disparities in longer wait times to a planned surgery. It’s important to do a sensitivity analysis as shown.

Proportional Hazards Assumption

Time-Race interaction term

Time Interval	Coefficient	HR (CI)
diagnosis to chemo interval	0.00127	1.001 (1.001 to 1.002)
surgery to chemo interval	0.0009	1.001 (1.000 to 1.002)

The proportional hazards assumption was barely significant, and parameter estimates were small. Interaction terms between time and race were still included in these models to account for the violations.

Models without interaction term

	diagnosis to chemo (without time-race interaction term)	surgery to chemo (without time-race interaction term)
	Adjusted HR (95% CI)	Adjusted HR (95% CI)
White	1.00 (Reference)	1.00 (Reference)
Black	0.784 (0.698 to 0.880)*	0.822 (0.732 to 0.923)*
Hispanic	0.946 (0.829 to 1.080)	0.989 (0.866 to 1.128)
Asian/Pacific Islander	0.863 (0.760 to 0.981)*	0.848 (0.746 to 0.964)*

HR=Hazard Ratio. CI=Confidence Interval.
* = Statistically Significant.
All models are fully adjusted for sociodemographic and clinical covariates

Without the interaction term, the wait times are less for Black and Asian (but still significant), and the Hispanic wait time for the diagnosis to chemotherapy interval is no longer significant.

Improvement of Fit
Akaike Information Criterion (AIC) and -2 log likelihood were checked between null models and full models.

	Diagnosis to Chemo		Diagnosis to Surgery		Surgery to Chemo	
	AIC	-2logl	AIC	-2logl	AIC	-2logl
Null model (intercept only)	64850	64850	48287	48287	64829	64829
Full model	64275	64229	48166	48124	64140	64094

Likelihood Ratio; Score; Wald chi-square : <0.0001

Ties handling: checked Efron, Breslow, Exact, and results did not differ.

APPENDIX G. Paper 3 Analytic Methods

Quasi-experimental research methods are designed to evaluate the causal effects of a non-randomized intervention, policy, or natural experiment. Three such designs were considered for evaluating the effect of the guideline of interest on timely adjuvant chemotherapy receipt: 1. difference-in-difference (DID), 2. regression discontinuity design (RDD), 3. interrupted time series (ITS). These methods are designed to minimize bias by use of treatment/control groups and/or accounting for secular trends. The table below summarizes these methods with descriptions and considerations for each method.

Research Design Considerations	Description	Control Group Required	Details	Decision Regarding Study Design for Paper 3
difference-in-difference (DID); difference-in-difference-in-difference (DDD)	*Difference 1:* before/after difference in outcome for intervention group *Difference 2:* before/after difference in outcome for control group *Difference 3:* Difference between Difference 1 and Difference 2 (this is the DID). Option to assess disparities: an interaction between pre/post time period, treatment status, and race (DDD estimates).	Yes. Considered age 80+ patients as control group since guideline specifically applies to those below age 80 (intervention group).	This design assumes parallel trends of outcome between the intervention and control groups prior to the intervention, which need to be tested.	Did not use this method due to challenges in finding a suitable control group (80+ group not suitable due to potential spill-over/cross-over with intervention group that can't be measured).
regression discontinuity design (RDD)	Uses an arbitrary cut-off point that determines treatment and control status. The design focuses on subjects around the cut-off point, where confounders are likely to be similar for treatment and control patients.	Yes. Considered ages 81-84 for control group and ages 76-79 for intervention group.	Options include sharp design where the cut-off perfectly determines exposure (proportion exposed changes from 1 to 0 at the cut-off) or fuzzy design, which allows for cross-over between treatment and control around the cut-off.	Did not use this method due to challenges in finding a suitable control group (80+ group not suitable due to potential spill-over/cross-over with intervention group that can't be measured).

interrupted time series (ITS)	Allows for analysis of: 1.the step/level change or immediate shift in population rates between the pre/post guideline period and 2. the change in slope between the pre-guideline and post-guideline trends to assess sustained effects (if any) in the post-guideline period. Effects of the intervention can be distinguished from secular trends.	Not required, but can include one provided a suitable control group is available.	Considerations: history (competing interventions that occurred at the same time as guideline); changes in instrumentation (outcome measure changes); selection bias (i.e. if population characteristics changed at the same time as guideline)	This method was used for Paper 3 analysis. Secular trend is accounted for, a control group is not required, and no obvious challenges with history, instrumentation, or selection bias during guideline endorsement.

The DID is a comparison of pre/post intervention differences in the treatment group and in the control group. The treatment and control groups are expected to have parallel trends of the outcome prior to the intervention, so that differences in each group after the intervention is compared to assess the effect of the intervention. It is also possible to assess racial/ethnic differences (DDD). The RDD uses an arbitrary cut-off point to determine treatment and control status and focuses on the subjects right around the cut-off point. The idea of the RDD is that the intervention and control groups around the cut-off are similar on confounders and the main difference between these two groups is that one gets the intervention and one does not, based on this arbitrary cut-off. In this specific case, the cut-off was 80 years of age.

DID and RDD methods both require a control/comparison group that was not exposed to the intervention to serve as a counterfactual for what would have happened if the intervention/guideline had not occurred. The control group characteristics should be as similar as possible to the exposed group (exchangeability), or balanced using matching methods, ideally differing only in exposure, and observed over the same period of time. Differences between exposed and unexposed groups should represent changes specifically due to the exposure.

When the DID approach was considered as an initial research design for this study, the control group considered was those ages 80+ since the guideline specifically applies to those under the age of 80. For RDD, ages 76-79 were considered for the treatment group (just below the age 80 cut-off) and ages 81-84 were considered for the control group (just above the cut-off). However, as was later determined, the 80+ group was not a suitable control group, since actual exposure to the guideline or doctor's use of the guideline cannot be ascertained. The guideline is a recommendation, not a strict protocol or policy; therefore, it is possible this guideline was used to treat those over the age of 80 or not considered in treating those under the age of 80, creating the issue of spill-over/cross-over between the treatment and control groups. While a fuzzy RDD, as opposed to a sharp RDD, allows for cross-over between treatment and control groups, it

was not possible to measure how much cross-over there was between the under 80 and 80+ age groups (i.e., what % of the 80+ group around the cut-off was exposed to this guideline). Those in the immediate neighborhood of the cut-off on both sides may have had similar exposure to this guideline, and there was not necessarily a way to measure this.

In addition, the decision to treat a patient with chemotherapy is determined by comorbidities and life expectancies, not necessarily just age. It is also possible this guideline could have potentially increased timely chemotherapy rate in the under 80 group while also influencing continued decrease in the 80+ rate, so that there would be two intervention groups affected by the guideline, and no actual control group. Due to the challenge of finding a suitable control group to assess the impact of the guideline of interest, a quasi-experimental method that does not require a control group, but still accounts for secular trends (ITS) was chosen for Paper 3 analysis. ITS has been used in other studies assessing the effects of a guideline without a control group. Paper 3 analysis estimated shifts in trends of timely chemotherapy receipt between the pre-and post-guideline time periods, while accounting for secular trends.

Cohort Selection Criteria

SEER-Medicare Study Selection Flow Chart, 2004-2013	
1. Stage III colon cancer diagnosis between 2004 and 2013 (excluding 2005 Louisiana cases), ages 66 - 79 years (guideline applies to those below 80 years of age)	N=17,158
2. Not diagnosed at autopsy and not diagnosed at death certificate	N=17,077
3. First and only cancer or first of more than one cancer diagnosis	N=15,989
4. Had surgical resection	N=15,962
5. Likely to have complete claims	N=9,749
6. Had a surgical resection claim in Medpar	N=9,026
7. Alive within 4 months of diagnosis	N=8,349
8. Resection admission not before diagnosis date	N=8,262
9. Resection admission not 12 months after diagnosis date	N=8,212
10. Chemotherapy not received before diagnosis date or before resection admission	N=8,080
11. No small race/ethnicity categories	**N=8,041**

Sensitivity analyses: ITS yearly time trend 2004-2005 drop

Initially a yearly time trend was considered for this analysis. Sensitivity analyses were conducted to check the reduced rates for all race/ethnicities from 2004-2005 for artifacts in data collection and chemotherapy coding changes.

Louisiana registry
2005 cases from the Louisiana registry were excluded from the study due to issues with data collection after Hurricane Katrina. Sensitivity analyses were conducted by dropping Louisiana cases for all years to assess whether trends remained the same or also had a similar drop as 2004-2005 for the other registries and years.
Results: The trend stayed the same as before when just 2005 Louisiana was dropped. Rates from other years don't drop as a result of completely excluding Louisiana registry. Therefore the 2004-2005 drop in rate is not due to dropping the 2005 Louisiana cases. As a result, the original cohort was kept and only 2005 Louisiana cases were excluded.

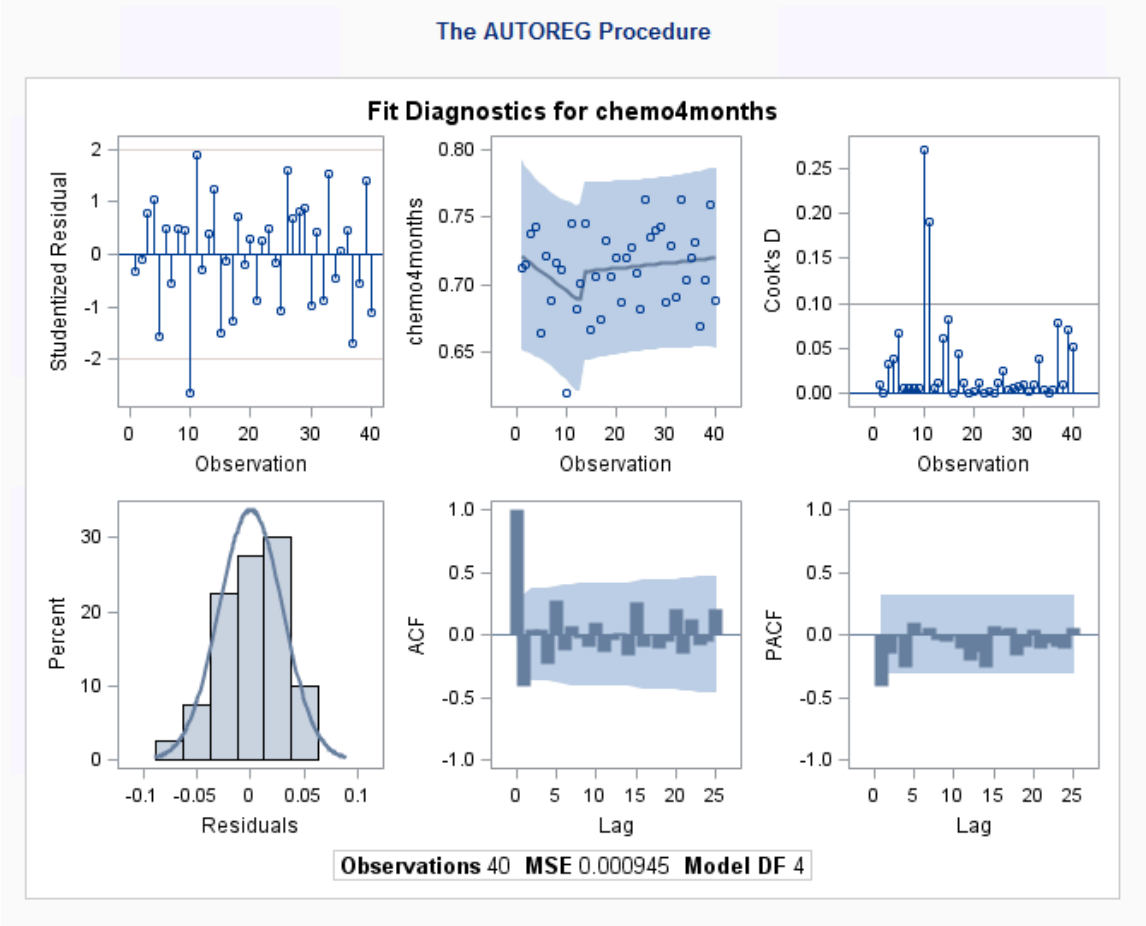
Large registry trends
Trends for each of the largest registries were checked separately: Greater CA, New Jersey, Kentucky, Greater Georgia, Louisiana, Iowa, Los Angeles, Detroit. Out of the 8 largest registries, 5 are showing rate drops between 2004 and 2005, and 2 are not showing the drop.

Chemotherapy coding changes
Coding changes for chemotherapy that occurred between 2004 and 2005 were checked, as detailed in Appendix C.

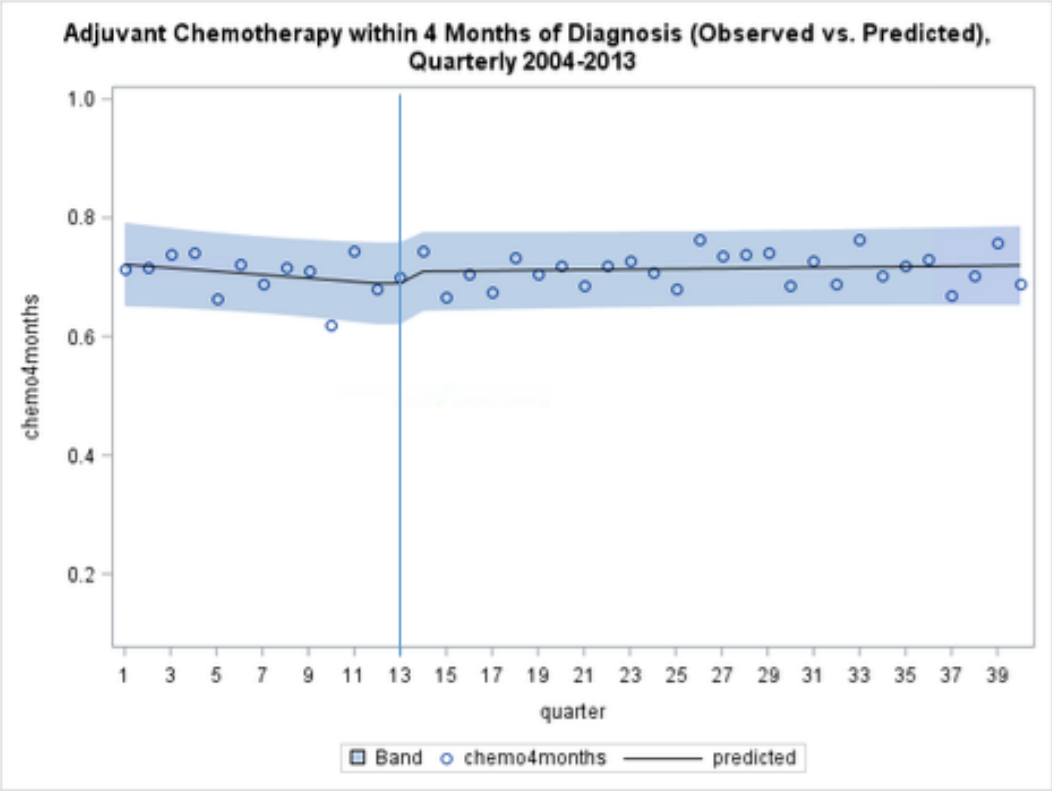
Conclusion: The following did not influence the 2004-2005 drop in chemotherapy rates - exclusion of 2005 Louisiana cases, large registries, chemotherapy coding changes.

ITS quarterly time trend
Time period considerations: yearly vs. quarterly. Results did not differ whether time was operationalized as yearly or quarterly. Quarterly time points were used for the final analysis, in line with the recommendation to have at least 8 time points before the intervention and 8 time points after the intervention to have sufficient power for an ITS analysis [72].

Quarterly trend fit diagnostics



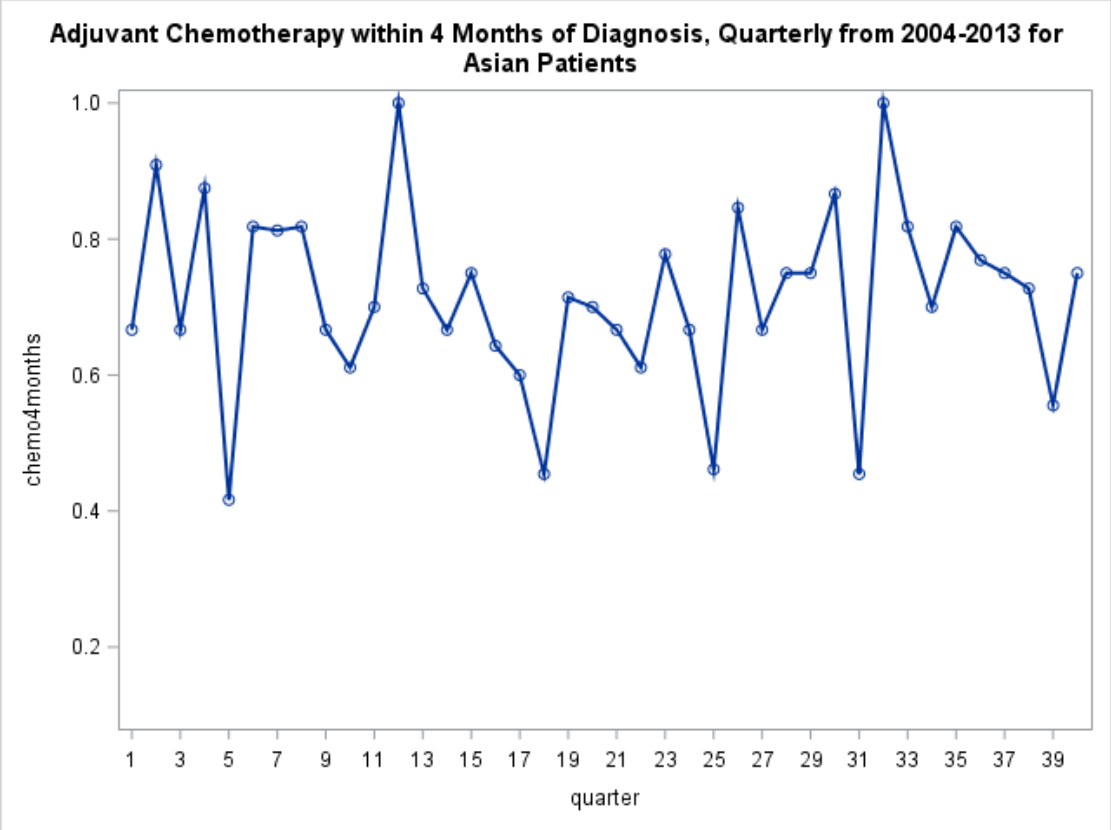
Quarterly trend observed vs. predicted



Asian and Hispanic Quarterly Trends

Unadjusted quarterly trends for these groups were not shown in paper 3 due to small cell sizes in the quarters.

Quarterly trend for Asian/Pacific Islander patients



Quarterly trend for Hispanic patients